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Pulmonary Arterial Hypertension In Congenital Heart Disease Could it be Normalized ? 11 years prospective study (2010-2021)

Rasmia H. Feituri [*1,2,3], Mariam El maadani [1,2,3], Hanan El Megasbi [1,2,3], Amal Khazmi [1] , Ibrahim Nabous [3]

[1] *Benghazi Cardiac Center.*
[2] *Al Hawary Hospital Benghazi.*
[3] *Benghazi University.*

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الملخص:

ارتفاع ضغط الشريان الرئوي يكون 25 مليميتر زئبقي أو أكثر في التشوهات الخلقية للقلب نتيجة لزيادة تدفق الدم للرئتين، أو نتيجة لتقلص الشريان الرئوي، أو نتيجة للإثنين معاً". دراسة مستقبلية لـ 68 من الأطفال والمراهقين والبالغين الذين لديهم ارتفاع في ضغط الشريان الرئوي المترددين في عيادات التشوهات الخلقية للقلب في مستشفى الهواري العام ومركز الوطني للقلب وكانت أعمارهم تتراوح ما بين الستة أشهر إلى الأربعين عاماً بين 6 /2010 و6/ 2021 وأستبعد أربع حالات الضغط ليس بسبب التشوهات الخلقية ومتابعة 64 المرضى المتبقية في المدة ما بين ثلاث أشهر إلى الإحدى عشر عاماً عن طريق الفحص السريري وتخطيط صدى القلب عبر الصدر، والقسطرة التشخيصية، وقد تبين بأن عدد الإناث أكثر عدداً بنسبة بسيطة 1.3 :1 وقد تبين أن سبب الضغط الرئوي كان 48.5% نتيجة فتحة بين البطينين، 28% قناة ما بين الاذنين والبطينين و8.5% فتحة بين الاذنين، 4.5% خروج الأوردة الرئوية من مكان غير الأذين الأيسر 3% انعكاس الشرايين ، 3% تشوهات مركبة، 1.5 % بطين واحد 1.5% القناة الشريانية السالكة و 1.5% ضيق في الصمام المتر الي. وقد كانوا 34% من متلازم الدوان. الأدوية المخفضة للضغط الرئوي التي استعملت: 37 حالة أخذو فياجرا وحالة واحدة بوزنتان، وثلاثة أخذو العلاجين معاً. عند المتابعة قمنا بتقسيمهم المرضى 64 الى مجموعتين المجموعة الاولى عددهم 34 مريض اعمارهم عامين او اقل والمجوعة الثانية عددهم 30 مريض أعمارهم أكبر من عامين. بتبين أن: المجوعة الأولى 34/28 (82%) رجع الضغط الرئوي إلى المستوى الطبيعي 28/26 بعد إجراء جراحة القلب لتصليح التشوه وأخذ العلاج. أما في المجموعة الثانية 10% فقط رجع الضغط إلى المعدل الطبيعي بعد إجراء جراحة للقلب لهم وأخذ العلاج. تبين أنه أفضل طريقة لعلاج الضغط الشريان الرئوي نتيجة التشوهات الخلقية للقلب هو أخذ العلاج وإجراء جراحة مبكرة قبل السنتين من العمر.

الكلمات المفتاحية:

ضغط الشريان الرئوي؛ التشوهات الخلقية للقلب. فياجرا، التدخل الجراحي للقلب.

Abstract

Objective: To recognize the effect of early surgical intervention in congenital heart in improving pulmonary hypertension, and to show the result of using medication in decreasing pulmonary hypertension **Background** : Pulmonary hypertension is defined as a mean pulmonary arterial pressure ≥25 mmgh .in congenital heart disease (PAH-CHD)it is caused by pulmonary overcirculation, pulmonary vasoconstriction, and pulmonary vascular disease, either alone or in combination. **Design** prospective clinical trial study with follow up. **Setting**: Al-Hawary General Hospital, National Benghazi Cardiac Center. **Methods:** 68 patients have been seen with pulmonary hypertension due to congenital heart disease in the period from 6/2010-6/2021, Age: from 6 months to 40 years old, We exclude 4 patients with primary pulmonary hypertension, we used clinical criteria, echocardiogram, and cardiac catheterization**. Follow up method**: period **3 months – 11 years,** 4/68 patients lost their contact, we divide the other 64 patients into two the groups; Group 1 (n= 34) ≤2 years old , Group 2 (n= 30) >2 years old. **Results: Gender:** F: M ratio is approximately 1.3 :1. The type of congenital heart disease was in (48.5%)of patients VSD, in (28%) AVC, (8.5%)ASD, (4.5%) TPVDA, (3%) TGA, (3%) complex,(1.5%) univentricle, (1.5%) PDA,(1.5%) intramitral valve membrane MS. (34%) were Down syndrome patients, 37/68 received sildenafil , 1/68 Bosentan, and 3/68 received both drugs. **Follow up results: Group 1 28/34 (82%) PHT normalized**, 26/28 post operative, **Group2 results:(10%) PHT normalized** after surgery**, Conclusions:** The best therapy for PAH-CHD remains prevention through a "timely" repair of the defect., advanced medications are required.

Keywords: pulmonary arterial hypertension, congenital heart disease, sildenafil, surgical intervention.

1. INTRODUCTION

Pulmonary hypertension is defined as a mean pulmonary arterial pressure ≥25 mmgh.**WHO clinical classifications of pulmonary hypertension:**

Group 1 - Pulmonary arterial hypertension (PAH) Group 2 - Pulmonary hypertension due to left-sided heart disease (PAH-CHD). Group 3 - Pulmonary hypertension due to lung diseases and/or hypoxia. Group 4 - Chronic thromboembolic pulmonary hypertension (CTEPH)

Goup -2 Pulmonary arterial hypertension (PAH) is a frequent complication of congenital heart disease (CHD), (PAH-CHD) particularly in patients with left-to-right (systemic-to-pulmonary)

*Correspondence:

Rasmia Husni Feituri.
rasmia_f@yahoo.com

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shunts. Persistent exposure of the pulmonary vasculature to increased blood flow and pressure may result in vascular remodelling and dysfunction. This leads to increased pulmonary vascular resistance (PVR) and, ultimately, to reversal of the shunt and development of Eisenmenger's syndrome. First described by Victor Eisenmenger in 1897 **[1]**, Eisenmenger's syndrome was defined in 1958 as "pulmonary hypertension at systemic level due to high PVR with reversed or bidirectional blood flow through a septal defect" **[2]**. Eisenmenger's syndrome represents the most advanced form of PAH-CHD. The current European Society of Cardiology guidelines provide an anatomical–pathophysiological classification of the congenital left-to-right shunts associated with PAH **[3]**. Simple defects include pre-tricuspid shunts (such as atrial septal defect (ASD)) and simple post-tricuspid shunts (including ventricular septal defects (VSD)), while complex CHD includes complete atrioventricular septal defect (AVSD), truncus arteriosus, single ventricular physiology with unobstructed pulmonary blood flow and transposition of the great arteries with VSD. In some instances, left-sided lesions can result in development of post-capillary pulmonary hypertension; however, this occurs much less frequently than PAH resulting from left-to-right shunts **[4]**.The development of PAH in patients with CHD is associated with increased mortality and high morbidity, reflected in a substantial increase in health service utilisation **[5, 6]**. While successful early closure of a cardiac defect prevents the development of PAH, and advances in paediatric cardiology and surgery have led to a marked decrease in the prevalence of PAH-CHD in western countries, the number of patients with CHD surviving into adulthood has increased [7, 8]. However, not all patients have a fully successful repair and many continue to suffer from residual lesions and potentially serious sequelae into adulthood. Depending on their age at closure, even patients who have had a full repair of their cardiac defect are at risk of developing PAH. In addition, there remains a population of patients with left-to-right shunts who are not diagnosed until childhood or even into adulthood. In these patients, changes to the pulmonary vasculature have already occurred, and PAH has, to a greater or lesser degree, already developed.

Among them are patients with Down's syndrome, who represent a significant and under-recognized patient group. Patients with Down's syndrome have a high incidence of complex cardiac defects and are at particular risk of developing PAH-CHD. In fact, in a recent registry study, individuals with Down's syndrome made up almost half the total population of Eisenmenger's syndrome patients [9]. Despite this, there is evidence that Down's syndrome patients are often undermanaged in terms of their PAH-CHD [9]. Today, the majority of patients with CHD seen in clinical practice are adults, and it is likely that they will continue to represent the largest proportion of patients requiring life-long medical care in the short-to-medium term [**10**, **11**]. The estimated prevalence of CHD is approximately six to 10 per 1,000 live births [**12**, **13**] and 4–15% of patients with CHD will go on to develop PAH [**14**]. In the French National Registry of PAH, PAH-CHD was the second most commonly associated form of PAH (after connective tissue disease-associated PAH) [**15**]. Data from European registry studies give the overall prevalence of PAH in adult patients with CHD as 4–28% and the prevalence of Eisenmenger's syndrome as ~1–6% [**14**, **16**]. The prevalence of PAH in patients with CHD varies according to the size and location of the cardiac defect [**3**]. The risk of developing Eisenmenger's syndrome also varies depending on the underlying heart defect, ranging from ~10–17% in patients with an ASD (pre-tricuspid shunt), to ~50% of patients with a VSD (post-tricuspid shunt), 90% of those with unrepaired AVSD and almost all patients with truncus arteriosus [**14**, **17**, **18**]. In general, patients with large and complex defects are at greatest risk. Patients with a post-tricuspid shunt (*i.e.* VSD, aortopulmonary window or complex CHD) tend to have an earlier onset of Eisenmenger's syndrome, with most patients presenting in childhood, compared with pre-tricuspid shunt patients (*i.e.* ASD or unobstructed anomalous pulmonary of patients with complex anatomy (*i.e.* AVSD, univentricular heart, transposition of the great arteries venous return) who generally do not develop pulmonary hypertension at all or present with PAH in adulthood [**19**]. Mortality and common arterial trunk) is higher than in those with simple anatomy (*i.e.* ASD, VSD or patent arterial duct). In a study of patients with Eisenmenger's syndrome at a specialist adult CHD centre, 50% of patients with simple anatomy were still alive at 58 yrs of age compared with 50% of patients with complex anatomy having died by the age of 42 yrs [**20**].

In 1998, during the Second World Symposium on Pulmonary Hypertension (PH) held in Evian, France, a clinical classification of PH was proposed.[**2**]

PATHOPHYSIOLOGY OF PAH-CHD

The timing of corrective surgery is critical to the avoidance of pulmonary vascular disease and PAH. The development of changes in the pulmonary arteries arising from persistently increased pulmonary pressure is a dynamic and multifactorial process, with progressive endothelial dysfunction leading to the characteristic vasoconstriction and remodeling of the pulmonary vascular bed [**22**].

TREATMENT OF PAH-CHD

When considering therapy in patients with PAH-CHD, care needs to be taken to obtain a full and detailed history including chronological symptom presentation. This is particularly important in the assessment of functional class. This can have a significant impact on the ability of Eisenmenger's syndrome patients to take part in day-to-day activities [**30**, **33**].

General management of PAH-CHD

General measures include avoidance of strenuous exercise, although mild activity is beneficial, and prevention of dehydration. Patients with Eisenmenger's syndrome are at particular risk during anesthesia and surgery, and special care is required. Pregnancy is contraindicated in patients with Eisenmenger's syndrome as there is a high risk of maternal and fetal mortality; adequate contraception is, therefore, mandatory. Long-term supplemental oxygen therapy at home may improve symptoms. However, as this has not been shown to modify survival, at least when given only at night [**36**],

Routine phlebotomy should not be performed as secondary erythrocytosis is beneficial for oxygen transport and delivery [**3**]. If moderate-to-severe symptoms of hyperviscosity are present, and iron deficiency and dehydration have been excluded, phlebotomy with isovolumic replacement should be performed carefully when the haematocrit is >65% [**38**]. Iron deficiency has been shown to be associated with a higher risk of adverse outcomes (all-cause mortality, transplantation and hospitalisation due to cardiopulmonary causes) in Eisenmenger's syndrome

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patients [**39**] and iron replacement therapy improves exercise tolerance and QoL [**40**]. However, care should be taken in patients with low oxygen saturations to avoid haemoglobin levels becoming too high [**39**].

Management of PAH-CHD with PAH-specific therapies

(bosentan, sildenafil or epoprostenol) treatment of PAH-CHD patients with PAH-specific therapy improves outcome. Long-term PAH-specific therapy in patients with Eisenmenger's syndrome has been shown to improve both objective exercise capacity and subjective symptoms, although escalation of therapy over time may be required if symptoms deteriorate during treatment [**41**].

"TREAT-TO-CLOSE" CONSIDERATIONS

Correction of an underlying congenital heart defect in infancy can prevent the development of PAH-CHD; however, a proportion of patients with left-to-right shunts are not recognised until later in their life, when they already have changes to the pulmonary vasculature and increased PVR. In those patients with increased PAP and Q_p, but with a PVR within normal limits or only slightly raised, pulmonary vascular changes are likely to be minimal and the patient may benefit from surgery [**42**].

PAH-CHD IN DOWN'S SYNDROME

Down's syndrome (trisomy 21) is the most common chromosomal abnormality, with an estimated incidence of approximately 1.1 per 1,000 live births [**45**]. The incidence has been increasing in recent years [**46**]. Over the past few decades there has been a substantial increase in the life expectancy of children with Down's Syndrome, from around 12 yrs in the 1940s [**47**] to 35 yrs in the 1980s [**48**] to 60 yrs today [**49**, **50**]. Down's syndrome is strongly associated with the development of pulmonary hypertension, predominantly associated with upper airway obstruction and CHD. The prevalence of CHD in neonates with Down's syndrome is around 42–58%, with AVSD and VSD representing the most common defects [**9**, **50**–**52**]. A number of factors in individuals with Down's syndrome may contribute to the high rates of PAH reported in this population. Down's syndrome patients tend to have a high prevalence of the complex defects that are most commonly associated with PAH and, in particular, with Eisenmenger's syndrome. In addition, upper airway obstruction resulting from a range of pathologies, including tracheal stenosis and nasopharyngeal, oropharyngeal and subglottic compromise, is a common finding in patients with Down's syndrome, which may also contribute to the high prevalence of PAH in Down's syndrome patients [**53**]. There is also a high prevalence of pulmonary hypertension of the neonate among Down's syndrome patients, with an incidence of 1.2–5.2% in Down's syndrome neonates compared with the reported general incidence of 0.1% [**50**, **54**]. The reason for this is unclear.

As with Eisenmenger's syndrome patients without Down's syndrome, those with Down's syndrome have markedly reduced long-term survival, although there is no apparent difference in survival between Eisenmenger's syndrome patients with and without Down's syndrome [**55**]. However, when compared with other CHD patients, those with Down's syndrome are more prone to developing PAH earlier, probably due to a subtle endothelial dysfunction [**56**], and have worse functional capacity; both factors being associated with poorer long-term outcome [**9**, **41**, **57**]. Despite this, however, a recent registry study found that patients with Down's syndrome received significantly less PAH-specific treatment [**9**]. This may reflect the lack of clinical trials in Eisenmenger's syndrome in general, and in Eisenmenger's syndrome patients with Down's syndrome in particular, at the time the registry was initiated. Although there are no randomised controlled trials in Down's syndrome patients with PAH-CHD, data from open-label studies have emerged recently. Duffels *et al.* [**58**] reported stabilisation of the 6-min walk distance (6MWD) and QoL in Down's syndrome patients with PAH-CHD following a median of 22 months' bosentan therapy, although this was in contrast with a significant improvement in parameters in patients with PAH-CHD without Down's syndrome in the same study.

Aim of the study:

To identify the type of congenital heart disease that resulted in pulmonary hypertension in this study

To recognize the effect of early surgical intervention in congenital heart in normalizing pulmonary hypertension

To show the result of using drugs in helping decrease pulmonary hypertension pre and post surgical intervention

2. METHODS:

Prospective clinical trial study with follow up comparing the effect of early surgical intervention and appropriate medication in two group of patients with congenital heart disease; the first group were ≤2 years when they had their Surgery and the second group were >2 years.

68 patients seen in OPD of General Hawary hospital and Benghazi cardiac center with pulmonary hypertension due to congenital heart disease and were followed up in the period from 6/2010- 6/2021 included in the study Age of the patients ranged from 6 months to 40 years old We exclude 4 patients with primary pulmonary hypertension . All patient name, age, gender, address, was registered and all patient was examined and diagnosed by clinical examination, CBC, chest x-ray, ECG and Echocardiography, we used Echo machines: Philips IE 33, VIVID 3, 5, 7, and 9, and GE 59, Trans-esophageal echocardiography done for 4 patients to diagnose congenital cardiac lesion cause the PHT.

Clinical criteria for pulmonary hypertension : heave, loud S2, and long systolic murmur of tricuspid valve regurgitation , Clinical criteria for operable cases : sign and symptoms of heart failure, O2 saturation > 95, chest x-ray cardiomegaly. Echo criteria: dilated right side of the heart, tricuspid valve regurgitation , dilated main pulmonary artery , deceleration time less than 100 sec, pulmonary valve regurgitation. Surgical correction done in patients with significant interatrial shunt (Q_p/Q_s >1.5 or signs of right ventricular volume overload) and PVR <5 Wood units Follow up method : We divided the patients with PHT into 2 groups according to their age , Group 1 : at the age of ≤2 years, Group 2 : > 2 years.15/68 (22%) patients right side study catheterization done for them to confirm diagnosis of PHT and to perform O2 test by measuring aorta and pulmonary pressure pre and post 100 % oxygen inhalation for ≥15mins , and also QP/QS by taking Bl gases from SVC and MPA pre and post100 % O2 inhalation , and measuring the pulmonary vascular resistance (PVR), we used Philips , GE, and Toshiba machines 3/15 diagnostic catheterization done twice for them. the response to O2 inhalation test is by decrease in the mean pulmonary pressure for ≥ 10 mmgh

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Statistic package of social sciences (SPSS) version 23.0 was used for data entry processing and analysis.

3. Results:

68 patients with congenital heart disease develop pulmonary hypertension , 42/68 (62%) was from Benghazi and 26/68 (38%) was from outside Benghazi

Gender: 38 are female and 30 are male, with slightly more common in females

F: M ratio is approximately 1.3 :1 (see diagram 1)

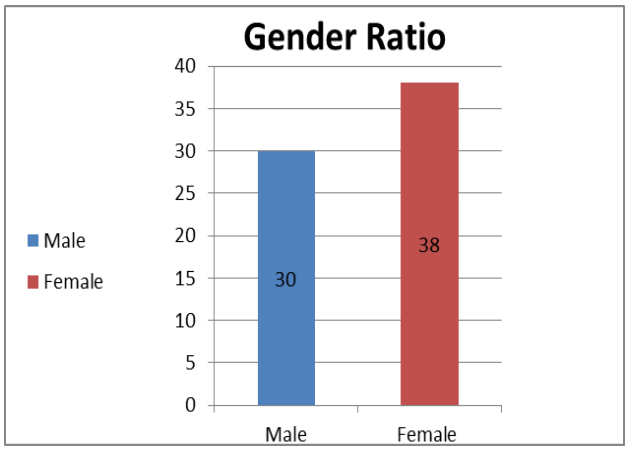


Diagram 1: ratio in PAH-CHD

Type of the congenital heart disease:

33/68 (48.5%) had VSD, 19/68 (28%) AVC, 6/68 (8.5%)ASD, 3/68 (4.5%) TPVDA, 2/68 (3%) TGA, 2/68 (3%) complex, 1/68 (1.5%) univentricle, 1/68 (1.5%) PDA, and 1/68 (1.5%) intramitral valve membrane MS. (see diagram 2)

23/68 (34%) were Down syndrome patients

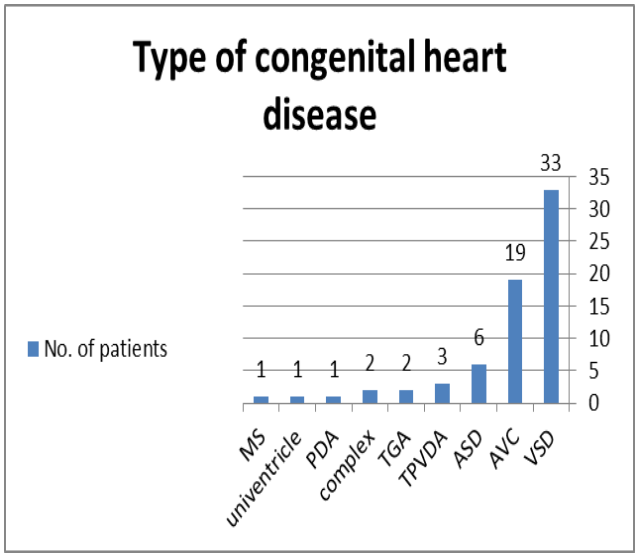


Diagram 2: Number of the patients with PAH according to the types of CHD

Medical Treatment: 64/68 received treatment

60/64 received sildenafil, 1/64 Bosentan, 3/64 both (see diagram 3)

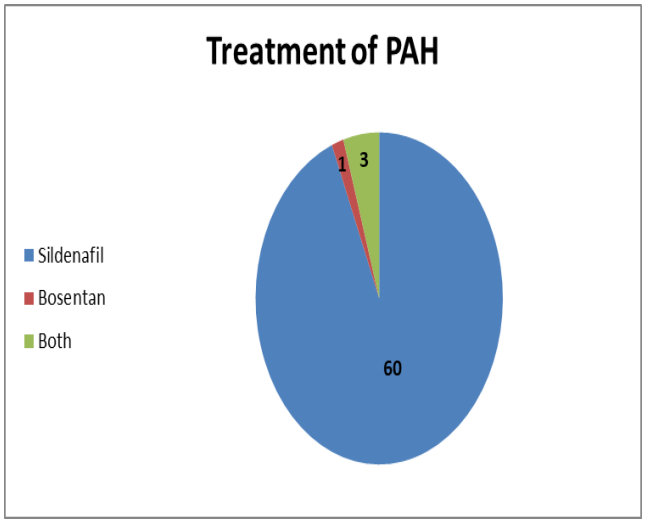


Diagram 3: no of patients received each type of medicine (PAH: pulmonary artery hypertension)

Follow up result:

We exclude 4/68 patients from follow up we lost their contact and follow up

Follow up n=64

7/64(17%) patients died, surgery was not performed for them

2/64 (3%) was having moderate VSD closed spontaneously and PHT normalized with help of medical treatment (sindenafil)

40/ 64 (62.5%) were operated : 3/40 died post operative (one after AVC correction, the other after double flap closure of VSD, one ASD with partial pulmonary veins drainage anomaly), **31/40 total correction** done for them and PHT normalized, **2/40 MPA banding** done first then total correction and PHT normalized, **3/40 only pulmonary artery banding** done for them still on medical treatment and sever PHT, **1/40 double flap** closure of VSD still on medical treatment still has sever PHT : (so 2 patients operated with double flap VSD closure one died and the other still has sever PHT)

14/64 (21.8 %) inoperable patients with PHT develop pulmonary vascular disease still alive but inoperable because of irreversible PHT **,**

1/64 (3%) operable PHT patients waiting for surgery

So 10/64 patients died (15.6%) , 7/11 without surgery, and 3/11 post operative

We divide the patients into 2 groups

Group 1 (n= 34) ≤2 years old , Group 2 (n= 30) > 2 years old

Group 1 n=34 (≤ 2 years old)

13 /34 (38%) are down syndrome (see diagram 4)

3/34 died before surgery 2 of them was down syndrome,**2/34 PHT normalized** after spontaneous closure and was on sildenafil. ,**1/34 still having PHT** on sildenafil waiting for surgery

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28/34 (82%) have been operated, In these patients with PHT pulmonary vascular changes are likely to be minimal and the patient got benefit from surgery, we depend on clinical criteria that they still have sign and symptoms of heart failure, O2 sat more than 95%, and cardiomegaly in chest x-ray , no cardiac catheterization done for them , 26/28 (92.5%) was total correction and the PHT normalized, 1/28 died after surgery, 1/28 develop CP after banding palliative surgery and PHT not normalized.

So 28/34 (82%) in this age group PHT normalized: (2 without surgery, and 26 (92.5%) post operative) ,4/34 died (11.7%) 3/4 before surgery and 1/4 after surgery, 1/34 (3%) waiting for surgery, 1/34 (3%) still has PHT post operative

Group 2 n= 30 (> 2 years old) (10/30 are down syndrome) **(see diagram 4)**

4/30 died without operation performed for them**,** 3/4 were patients with Down syndrome **12/30 operated** : **2/12 died** post operative, {one post double flab VSD closure at7 years old, the other total correction of TPVDA and ASD at 40 years old }.**3/12** PHT normalized after surgery operated at 2.5 yrs – 3.5 years old **.7/12** still having persistent sever PHT after surgery and on medical treatment 1/7 : 26years old female from Tubruk operated with double flab VSD closure she has also arrhythmia , 3/7 pulmonary artery banding : (5 yrs female from Benghazi with large VSD , 20 years old female from Baida with large VSD and 10 years old down syndrome boy from Egkera with AVC) , 2/7 post TGA 17 years old Palestinian girl lives in Benghazi the operation was arterial switch done at 1 year old, and the other 8 years old boy the operation was Senning , and 1/7 : 4 years old down syndrome female patient from Benghazi post ASD closure. **14/30 having sever PHT** on medical treatment**,** they develop pulmonary vascular disease still alive but inoperable because of irreversible PHT **,** with **Eisenmenger's** syndrome , **Complications:** 3/30 patients develop right side heart failure, 4/30 patients HCT > 65, Phlebotomy done for them

So only 3/30 (10%) PHT normalized in the age group > 2years old

None of the patients had their PHT normalized in the group operated after 3.5 years of age

6/30 died (4 without surgery, 2 post operative)

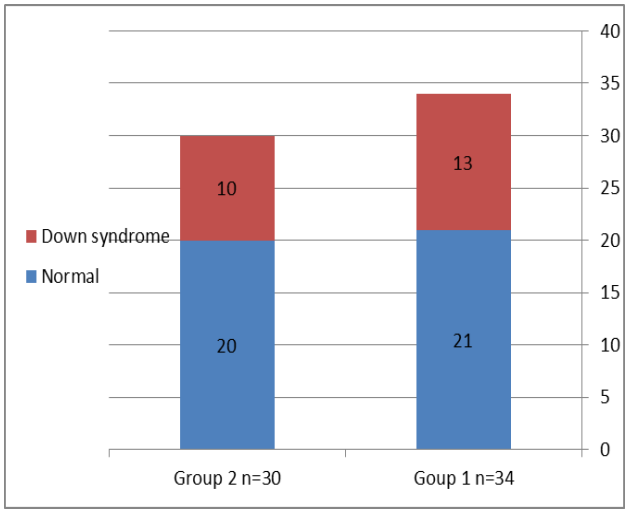


Diagram 4: Number of down syndrome patients in each group

Tab. 1: Follow up result of PAH-CHD patients comparing both Groups

PAH-CHD	Group 1	Group 2	Total
Died without surgery	3	4	7
Operated	28	12	40
Spontaneous closure	2	0	2
PAH not operated	1	14	15
Total	34	30	64
PAH normalized	28	3	31/64

Tab. 2: comparing follow up result of operated patients in both groups

Operated patients N=40	Group 1 no=28	Group 2 no=12	
Died post operative	1	2	
Still having PAH post operative	1	7	
PAH normalized post operative	26	3	P value 0.000
Total	28	12	

Using IBM SPSS Version 23 Chi Square test the P value was 0,000 therefore there is a strong association between the normalized PAH and the age of the patient at time of operation.

4. DISCUSSION :

Our study has shown that the pulmonary hypertension slightly more common in females

The most common defects associated with elevated pulmonary pressure is a large ventricular septal defect (VSD)[1,2,14,17,18] this is could be that the VSD is the most common congenital heart disease.

We had limited use of Cardiac catheterization we did for only 22% of the patients which is very important to detect the operable cases in severe PHT in older patient [21]

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In our study (34%) of the patients with pulmonary arterial hypertension had Down syndrome, Down syndrome patients are more prone to have pulmonary hypertension and must be treated and operated earlier than the other patients [9,49,50,51,52,53,56] Although mortality remained high, there was no significant difference in mortality between patients with and without Down's syndrome[55]

PHT is a chronic morbidity and fatal disease, in our study 10/64 (15.6 %) patients died [5,6], and 23/64 (36%) patients still alive with severe PHT not normalized (8 patients post operative, 14 patients inoperable, 1 waiting for surgery) and due to medical treatment they live more longer than before the oldest one was 40 years old which died post operative [7,19,20]

Pulmonary arterial hypertension can be normalized if medical treatment and early surgical intervention done, In these patients with increased PAP and Q_P, but with a PVR within normal limits or only slightly raised, pulmonary vascular changes are likely to be minimal and the patient got benefit from surgery[6] Furthermore, in follow-up examinations up to11 years, we found the beneficial effects of early medical treatment and surgical intervension .

In our study 25/34 (79%) patients of pulmonary hypertension normalized post operative in group of patients younger than 2 years old, and only 3/30(10%) of PHT normalized post operative in group of patients more than 2 years old [7,8,23,24]

In this study there are patients with delayed intervension with Eisenmenger's syndrome which leads to complication[1,2,7,9,19,32,36]

5. CONCLUSION :

Improvements in the diagnosis of CHD and its surgical and medical management have led to a significant increase in the number of patients surviving into adulthood. The best therapy for PAH-CHD remains prevention through a "timely" repair of the defect. The development of PAH, and particularly Eisenmenger's syndrome, in these patients is associated with increased morbidity and mortality. There is increasing evidence of the benefits of PAH-specific therapy in PAH-CHD in terms of improving exercise capacity, symptoms and survival. Nevertheless, mortality remains relatively high, and there is a need for new therapeutic options and strategies in this complex patient population. Specific issues exist with regards to the management of certain patient subgroups. For example, the assessment of operability and timing of corrective surgery in patients with complex defects and increased pulmonary pressures warrants further investigation, particularly with regards to the use of PAH-specific therapy as part of a treat-to-close strategy. Patients with Down's syndrome make up a significant proportion of the PAH-CHD population, but historically have not been managed optimally. There is a lack of clinical studies in these patients and, although new and encouraging data are emerging, there remains a need for further investigations.

Advance medication are required in our center to achieve better results

Overall, we are beginning to see progress in the management and treatment of patients with PAH-CHD; however, much still needs to be done to address the many issues involved in the management of this growing and complex patient group.

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