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Management of Pulmonary Arterial Hypertension Associated with Congenital Heart Disease in Children

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Abstract: *Background* Pulmonary arterial hypertension (PAH) is a serious complication of unrepaired congenital heart disease (CHD). The aim of this retrospective study was to evaluate the management of PAH associated with CHD (APAH-CHD) in the Iraqi Center for Heart Disease, Baghdad. *Methodology*Twenty children with APAH-CHD were surgically treated over 2 years (1st June 2013 to 1st June 2015).Clinical evaluation was followed by chest radiography and transthoracic echocardiography (TTE). Suspected inoperable patients were subjected to cardiac catheterization and Oxygen test. Total surgical correction was elected in children with mild to moderate PAH while young children with low body weight and severe PAH were offered pulmonary artery banding (PAB) reducing PA pressure to 50% of the systemic pressure. All patients were looked after carefully in the ICU. TTE was used in the follow up. *Results* There were 12 females (F: M=1.5:1) The ages ranged between 4 and 84 months with a mean of 16.4 ± 20.1 months. Seventy % were infants. Five patients (25%) underwent cardiac catheterization. Ventricular septal defect was the commonest underlying anomaly (90%). Twelve patients had full correction and they were significantly older than those treated by PAB. Three totally corrected kids died (25% death) whereas no child died after PAB. Pulmonary hypertensive crisis was accused once. The remaining 17 patients were followed up for 6-18 months; 14 were alive when this paper was written.*Conclusion*PAB may be a good option for the very young and sick children who might not tolerate a lengthy total correction.

Keywords: Pulmonary Arterial Hypertension, Associated, Congenital Heart Disease, Children, Eisenmenger's Syndrome, Pulmonary Artery Banding, Total Correction

1. Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease leading to right heart failure and ultimately death if untreated [1]. World Health Organization (WHO) defined PAH as pre-capillary pulmonary hypertension with a mean pulmonary artery pressure (m PAP) greater than or equal to 25 mm Hg with a pulmonary capillary wedge pressure (PCWP) less than or equal to 15 mm Hg. In children, PAH is often associated with a pulmonary vascular resistance (PVR) greater than 3 indexed Wood units [1] [2].A significant proportion of patients with unrepaired congenital heart disease (CHD), particularly those with systemic to-pulmonary shunts, eventually develop PAH [1]. The prevalence of PAH associated with congenital systemic-to-pulmonary shunts in Europe and North America has been estimated between 1.6 and 12.5 cases per million adults, with 25% to 50% of this population affected by Eisenmenger's syndrome (ES) [1]. Dr. Victor Eisenmenger, an Austrian physician described the history and postmortem details of ES in a man of 32 with ventricular septal defect (VSD) and cyanosis for the first time in 1897. In a two-part lecture published in the British Medical Journal on1958; Dr. Paul Wood ascribed a cohort of 127 VSD and non-VSD cases as Eisenmenger's complex. In addition, he assigned the first definition of ES as "pulmonary hypertension due to a high pulmonary vascular resistance with reversed or bidirectional shunt at aorto-pulmonary, ventricular, or atrial level". This

definition still stands today [2] [3].Although better understanding of pathophysiological mechanisms of PAH over the past quarter of a century has led to the development of new medical therapeutics, no cure for PAH exists and the prognosis remains unsatisfactory. PAH-CHD short of Eisenmenger's syndrome may be treated by surgical correction of the underlying CHD, pulmonary artery banding (PAB), balloon atrial septostomy or lung transplantation [1]. To the best of our knowledge, there are no true statistics or studies on the prevalence of APAH-CHD in Iraq. The aim of this retrospective study was to evaluate the management of APAH-CHD in a group of children in the Iraqi Center for Heart Disease (ICHD), Baghdad, Iraq with reference to similar studies elsewhere in the world.

2. Methodology

Over 2 year period (1st June 2013 to 1st June 2015); 20 children with APAH-CHD were studied. Suspected patients were assessed by a paediatric cardiologist and cardiac surgeon. Thorough history taking and physical examination was performed. Chest x-ray and trans-thoracic echocardiography (TTE) were routinely done. Suspected inoperable patients were subjected to cardiac catheterization and Oxygen test. 100% Oxygen was administered for 10-15 minutes; a decline of PA pressure of 10-20 mmHg indicated a good vasodilatation response. Patients failing to have such a response were considered inoperable. Preoperative medications included antibiotics, anti-failure drugs such as digoxin, frusemide and spironolactone besides modern drugs for PAH like Sildenafil and Bosentan.

Pulmonary artery pressure was directly and routinely monitored throughout the operation. Special anaesthetic measures were taken to reduce pulmonary hypertension such as 1. Giving high FiO_2 (100%) to induce dilatation of the pulmonary artery 2. Hyperventilation by increasing the respiratory rate and tidal volume to enhance CO_2 wash 3. Angised nebulization 25 mic/kg to induce PA vasodilatation and 4.Milrinone infusion 0.375–0.7 mic/kg/min to increase the right ventricular contractility.

Total surgical correction was elected in children with mild to moderate PAH secondary to CHD. The approach was via median sternotomy and cardiopulmonary bypass (CPB). Standard techniques were used to correct the underlying defects such as direct or patch closure of atrial or ventricular septal defect, ligation or division and suture of PDA.

Children with CHD and history of failure to thrive, severe recurrent chest infection or severe PAH as judged by TTE were offered PAB (Figure 1 a-c).Via median sternotomy, the pericardium was opened and both MPA and aorta were exposed. The MPA was encircled by 0 silk suture (to be used later for PAB). Features of severe PAH were observed (big PA, enlarged and hypertrophied right ventricle-RV-).The silk ligature was stabilized by few simple 5-0 Polypropylene sutures and then was tightened by applying hemoclips which were finally positioned according to the desired degree of PA narrowing. Banding aimed at reducing PA pressure to 50% of the systemic pressure under FiO_2 of 60% while maintaining the SpO_2 above 85% (Figure 2 a-b) and avoiding RV dysfunction or significant arrhythmias.

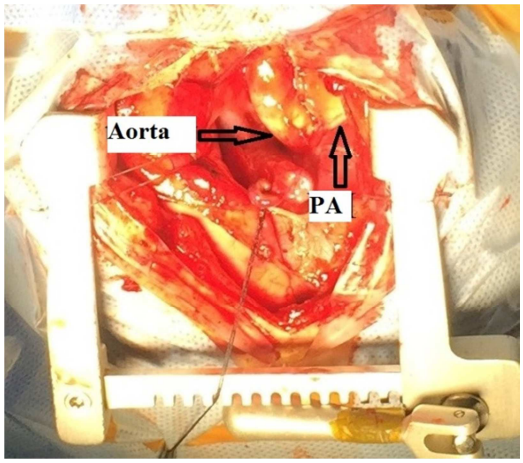

Figure 1a. *Exposure of PA and Ascending aorta prior to PAB in a child with VSD and severe PAH.*

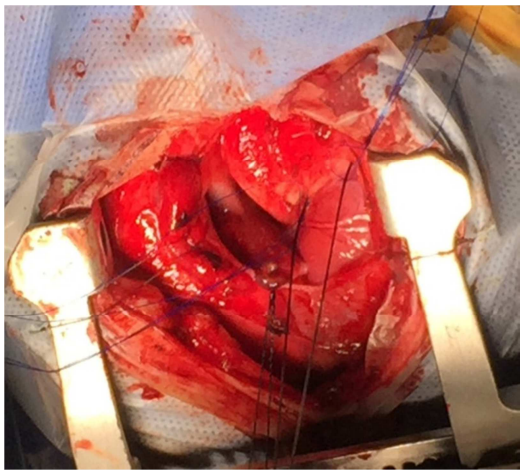

Figure 1b. *The patient above with a silk encircling the MPA prior to PAB.*

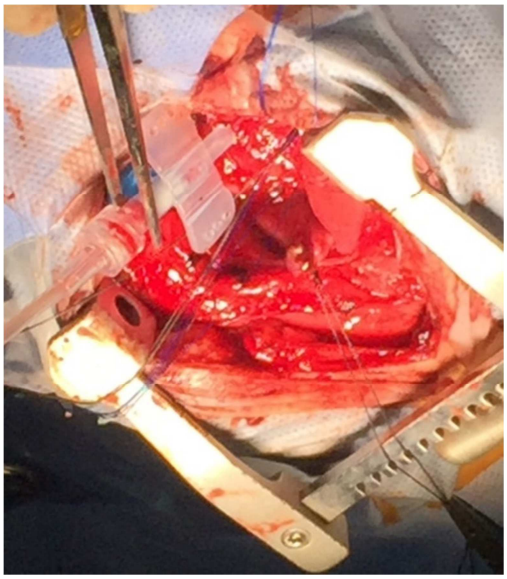

Figure 1c. *PAB has been completed with a needle in PA to measure the pressure after banding.*

Figure 2a. *Monitor readings prior to PAB in the patient above.*

Figure 2b. *Monitor readings after PAB; the PA pressure has been reduced to almost one third of the systemic pressure while the SpO2 was maintained above 85%.*

Postoperatively, the children were routinely admitted to the ICU for 24-48 hours and then transferred to the ward. Besides routine early complications after any open heart operation, special problems may develop such as persistent or sudden rise in PAP. Such events were diagnosed and managed accordingly when developed. TTE was done in the early postoperative period to check the integrity of total correction and pressure gradient across pulmonary artery band as well as during late follow up visits. Statistical Analysis was performed using Z Test for 2 population proportions and Student T-Test for 2 independent means.

3. Results

There were 12 females and 8 males (F: M= 1.5 to 1). The ages ranged between 4 and 84 months with a mean of 16.4 ± 20.1 months. The majority were infants; 14 out of 20 (70%) (Table1). Ventricular septal defect was the commonest CHD associated with PAH in this study (18 out of 20: 90%) whereas other lesions were less frequent. Sixty % of patients had full correction whereas others had PAB (Table 2). Children in this study elected for total correction were older than those treated by PAB. The age of kids who received total correction ranged from 7 to 48 months with a mean of 21.5 months. Whereas children received PAB aged between 4 and 9 months with a mean of 5.75 months. The difference was statistically significant. Most patients (n=17; 85%) stayed for 1 to 2 weeks (Table 3). In 5 patients, the degree of PAH was not mentioned in the medical files whereas most of the remaining patients (n=14) had severe degree of PAH (Table 4a and Table 4b). Five patients (25%) underwent cardiac catheterization; the details are shown in Table 5. The commonest underlying CHD was VSD (n=4, 80%) whereas 2 patients had PDA in association with VSD. All had severe degree of PAH. A good response to 10 minute O_2 test was reported in 3 patients in whom total surgical correction was advised accordingly. Moreover, a girl of 7 years had a trial to occlude a huge PDA but failed due to embolization of the occluder. The same patientunderwent patch closure of the VSD and ligation of the PDA 6 months later but unfortunately died in the first postoperative day due to a sudden rise in PA pressure.

In our study, three kids whose cardiac defects were totally corrected died making a death rate of 25% in this group whereas no child died among those managed by PAB (Table 6). However, this difference was not statistically significant. The overall death rate was 15% (3 out of 20 patients). The cause of death was known in one case only [pulmonary hypertensive crisis]. Unfortunately, there were not sufficient details in the medical files of other patients to pinpoint the cause of death. The remaining 17 patients were followed up for 6-18 months. At the time of writing this paper, 14 patients are still alive, 2 could not be reached while one child has recently died.

Table 1. *Age and Sex Distribution.*

Age (months)	Male n, (%)	Female n, (%)	Total n, (%)
1-6	2	4	6
7-12	2	6	8
13-24	3	1	4
25-36	0	0	0
37-48	0	0	0
49-60	1	0	1
61-72	0	0	0
73-84	0	1	1
Total	8 (40)	12 (60)	20 (100)

Table 2. *APAH-CHD vs. Type of Surgery.*

CHD	PA banding	Total correction	Hospital mortality
ASD	0	1	0
VSD	5	6	0
ASD+VSD	0	1	1
ASD+VSD+PDA	1	0	0
VSD+PDA	1	2	1
VSD+PS	0	1	0
AV canal defect	0	1	1
TGA	1	0	0
Total	8**	12**	3

** The result was not significant at $p < 0.05$ (Although 3 patients died following total surgical correction and none after PAB, but the difference was not statistically significant).

Table 3. *Duration of Stay in the Hospital.*

Duration (days)	Patients, n (%)
1-7	11(55)
8-14	6 (30)
15-21	0
22-28	0
56	1(5)
Unknown	2 (10)
Total	20 (100)

Table4-a. *Echocardiographic Findings vs. Surgical Therapy & OutcomePart I.*

Gender & Age	Underlying CHD	Degree of PAH	Surgical Therapy	Outcome
F, 5.5 months	VSD	Severe	PAB (SPAP reduced to 31 mmHg with SAoP of 90-120 mmHg)	Survived (TTE on the 2nd postoperative day was good)
F, 7 months	VSD	Severe	PAB (SPAP was reduced to 17 mmHg with SAoP of 90-110 mm Hg)	Survived (TTE on the 2nd postoperative day was good)
F, 5 months	2 VSDs, ASD & PDA	Severe (SPAP=49 mm Hg)	PAB (SPAP dropped to 29 mmHg)	Survived (TTE on the 2nd postoperative day was good with PG across PAB of 40 mmHg)
M, 14 months	VSD (12*15 mm)	Severe (PAB=Systemic arterial pressure)	Total correction	(Survived m PAP dropped to 50 mmHg on 5th postoperative day as measured by TTE. It became normal 11 months postoperatively.)
M, 7 months	Intermediate AV septal defect	Moderate	Total correction	Died
M, 11 months	VSD	Not specified@	Total correction	Survived
F, 9 months	TGA	Not specified	PAB	Survived (TTE 5 months later showed an effective PAB with PG of 60 mm Hg)
M, 4 months	VSD	Severe	PAB	Survived
F, 12 months	VSD	Not specified	Total correction	Survived
F, 3 months	VSD	Severe	PAB	Survived

Table 4-b. *Echocardiographic Findings vs. Surgical Therapy & Outcome Part II.*

Case, gender & age	Underlying CHD	Degree of PAH	Surgical Therapy	Outcome
F, 3 months	2 VSDs & PDA	Severe	PAB (SPAP dropped from 54 to 33 mmHg)	Survived (TTE on the 2nd postoperative day was good with PG across PAB of 70-90 mmHg)
F, 11 months	VSD & PDA	Severe	Total correction	Survived
F, 7 yrs	VSD & PDA	Severe	Total correction	Died
F, 10 months	ASD & VSD	Severe	Total correction	Died
M, 5 yrs	2 ASDs	Severe	Total correction	Survived
F, 10 months	VSD	Not specified	Total correction	Survived
M, 20 months	VSD (12*15 mm)	Severe (SPAP=AoP)	Total correction (T Epicardial E showed no residual leak)	Survived (TTEs done on 2nd& 6th postoperative days were good)
M, 7 months	VSD	Severe (SPAP/SAoP= 100:120 mmHg, M PA to Ao size=2.5:1)	PAB (PA:Ao size dropped to 1:1, SPAP: SAoP dropped to 70:100 mmHg)	Survived (TTE on the 2nd postoperative day was good with PG across PAB of 45 mmHg)
M, 11 months	VSD & PS	Not specified	Total correction	Survived
F, 8 months	VSD	Severe	Total correction	Survived

Table 5. *Findings in Patients Subjected to Cardiac Catheterization.*

Case	Underlying CHD	Degree of PAH	Response to 10 minute O_2 test	Comments
F, 11 months	Large VSD & PDA	Severe	There was a decline in m PA pressure by approximately one 1/3	The vasodilator test was positive; therefore closure of VSD & ligation of PDA was advised & done successfully.
F, 7 yrs	VSD & huge PDA	Severe	Urgent total surgical correction was advised & performed. The patient had unsuccessful trial of closure of the PDA 6 months earlier by an Occlutech ASD occluder 15 mm in size due to embolization of the occluder.	The patient died in the first postoperative day due to sudden rise in PA pressure.
M, 5 yrs	Two ASD secondum	Severe	Good response.	Total surgical correction was advised & done successfully.
M, 20 months	Large VSD	Severe	There was a significant change in pressure between aorta & PA.	Total surgical correction was advised & done successfully.
F, 8 months	Large VSD	Severe	Not mentioned.	Total surgical correction was advised & done successfully.

Table 6. *Mortality.*

Case	Age & Gender	CHD	PAH	Surgical therapy	Time & cause of death
1	7 yrs, F	Huge PDA & small VSD	Severe	Total correction (total CPB, ligation of PDA, closure of VSD by a pericardial patch through RA approach)	1st postoperative day due to sudden rise in PA pressure.
2	15 months, F	Small ASD secondum& large inlet VSD	Severe	Total correction(total CPB, direct closure of ASD, pericardial patch closure of VSD through RA)	6th postoperative day. No details relevant to cause of death reported in the medical file.
3	9 months, M	An intermediate AV septal defect, large ASD primum, moderate sized inlet VSD, clefted MV with severe MR	Moderate (m PA pressure=40 mmHg)	Total correction (total CPB, RA approach, single pericardial patch technique to close ASD & VSD and divide the common AV valve into 2 valves)	2nd postoperative day. No details relevant to cause of death reported in the medical file.

4. Discussion

4.1. Prevalence

The prevalence of PAH-CHD has fallen in developed countries over recent years due to advances in paediatric cardiology and surgery thus the number of patients with CHD surviving into adulthood has increased [4]. During the period of the study, 218 operations were performed for all CHDs in the ICHD; thus the ratio of APAH-CHD to all CHDs was 20: 218 (9.17%). Paediatric cardiologists accept 2%–10% as the percentage of patients with CHD who can progress into PAH [2]. Thus our figures are within the standard range.

4.2. Age & Gender

Most patients in this study (n=18, 90%) were infants (under 2-yrs old). This indicates that symptoms were severe enough to prompt early consultation and diagnosis.The female to male ratio in this study was 1.5:1. Similarly, in the Dutch registry, females had a 35% higher risk of PAH, an observation which has been noted previously [5]. The association of PAH with female sex is interesting. Idiopathic PAH is also much more common in females with a ratio of approximately 2.5:1. In adult CHD unit at Mayo Clinic, comprising over 4000 patients, the frequency of isolated secondum ASD with ES in women exceeded that in males by 28:1. Genetic susceptibility may contribute to the high female vulnerability for PAH [5].

4.3. Underlying CHD

Although PAH may occur in the context of a wide range of different defects, by far the largest proportion of patients with PAH have a septal defect [5] [6]. In the Dutch registry, PAH prevalence rates varied from 3% in patients with PDAs to 100% in patients with an aortopulmonary window [4] [6].

In the CONCORD study which involved more than 7000 patients with CHD, atrial and VSDs were the 2 most frequent defects in the whole series and these defects were associated with PAH more commonly than any other lesion [5]. The present study had exactly the same findings with VSD being the most frequent lesion associated with PAH (n=18; 90%) followed by ASD (n=4; 20%).

4.4. Influence of Type and Size of Cardiac Septal Defect

Only 10% of patients with unrepaired ASD develop Eisenmenger's syndrome compared with 50% of patients with unrepaired VSD and almost all patients with unrepaired truncus arteriosus [7]. Only 3% of patients with small to moderate VSD develop pulmonary vascular disease, whereas 50% of patients with a large VSD (> 1.5 cm diameter) will be affected. The exposure of the pulmonary circulation to elevated pressure and/or hypoxia also influences the risk of developing pulmonary vascular disease [7].All VSDs in this series were large favoring the development of severe PAH through increased pulmonary blood flow.

4.5. Work Up

Echocardiography is central to the diagnosis and management of APAH-CHD [8]. It was done to all patients in this series and was very useful in making a diagnosis of the underlying CHD as well as assessment of the degree of PAH (mild, moderate or severe). In 5 patients, the degree of PAH was not mentioned in the medical files whereas almost all remaining patients (n=14) had severe degree of PAH.

4.6. Cardiac Catheterization

Cardiac catheterization remains the gold standard for diagnosis of PAH [8]. Measuring the response to pulmonary vasodilators such as oxygen is an important component of the procedure as it guides therapeutic planning [8]. The most recent consensus defines a positive response as a decrease in mean PA pressure by≥10 mm Hg to≤40 mm Hg with an unchanged or increased cardiac output [8]. In this series, 5 patients had cardiac catheterization which revealed a positive response to 10 minute O_2 test in 3 occasions. Any procedure performed on a patient with PAH brings with it an increased risk of cardiopulmonary collapse and must be performed thoughtfully and with maximal available expertise [8].

4.7. Type of Surgery

The best therapy for APAH-CHD is 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 and hence; it is a contra-indication to surgery [4] [6]. In this study, patients considered operable received total correction (for older children) or PAB (for the very young with severe PAH in whom total correction thought to carry higher risk).

4.8. Total Surgical Correction vs. PAB

Within the last two decades, early definitive intra-cardiac repair has largely replaced palliation with PAB. This trend has evolved because many centers have demonstrated improved outcomes with primary corrective surgery as an initial intervention in the neonate with CHD [8]-[11]. Children in this study elected for total correction were significantly older than those treated by PAB. Pulmonary artery banding is a technique of palliative surgical therapy used by congenital heart surgeons as a staged approach to operative correction of congenital heart defects.

4.9. PAB: Our Impression

All patients in this group had a good response in term of an immediate drop in PA pressure and a change in the size of MPA compared to aorta; this response was confirmed by echocardiography done in the early postoperative period. None of the children died in the early postoperative period compared to 3 among those receiving total correction (25%). Long-term follow-up was available in one patient in whom TTE done 5 months postoperatively revealed an effective PAB with pressure gradient of 60 mm Hg.

We think PAB was life-saving for those little children with large septal defects and severe PAH who might not have tolerated total correction if it was offered for them in place of PAB. Similarly, in South America, PAB remains a common strategy for patients with late presentation and elevated pulmonary vascular resistance [2].

4.10. Mortality

The development of PAH in patients with CHD is associated with increased mortality and high morbidity [4]. Survival of children with Eisenmenger's syndrome appears to be worse than that reported in adults [12]. A pulmonary hypertensive crisis was the cause of death in one patient in this series while it was unknown in the remaining two.

4.11. Late Follow Up

In this study as in other studies on APAH-CHD, many patients are likely lost to follow up, especially upon completion of the repair [3]. We tried to arrange a TTE to our patients 6 months-2 years after surgery by contacting them via phone calls but unfortunately most of them were non-compliant. Socioeconomic factors could be responsible for that as most of them were poor and living in areas remote from the hospital.

5. Conclusion

In view of low mortality associated with PAB vs. total surgical correction for treatment of APAH-CHD, we think PAB may be a better surgical option particularly for the very young and sick children who might not tolerate lengthy operation such as total correction.

Recommendations

There is a need to carry out an epidemiological study to find the prevalence of APAH-CHD in Iraq. Such a study is vital to know the magnitude of the problem and to guide the national health services and resources accordingly. Prevention of PAH in patients with CHD (by surgical repair of the shunt prior to the onset of pulmonary vascular disease), and the treatment of existing PAH (by surgery or medical management) is highly recommended. The modern PAH specific drugs should be made available so that APAH-CHD patients are managed in a proper medical regimen before considering surgery. Expertise in the management of this difficult complication of CHD needs to be built by communication with international centers specialized in this field.

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