Pulmonary Hypertension in Apparently Healthy Children in Southern Nigeria

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ABSTRACT

Objective: To determine the severity and prevalence of pulmonary hypertension and its relationship with age and body mass index (BMI) in healthy children.

Study Design: Observational study.

Place and Duration of Study: University of Nigeria Teaching Hospital Ituku-Ozalla Enugu, Lagos State University Teaching Hospital, Niger Delta University Teaching Hospital, Bayelsa and Blessed Children Hospital Enugu from January 2010 to December 2019.

Methodology: Four hundred and seventy (470) apparently healthy children aged 1 to 17 years underwent Doppler echocardiographic studies. Their tricuspid regurgitation velocity (TRV) was measured with continuous wave Doppler. Pulmonary artery systolic pressure (PASP) was estimated using the Bernoulli equation. Elevated PASP were determined at PASP ≥35/mmHg. Values were compared against age and BMI.

Results: The mean age was 7.9 ± 3.3 years. Four hundred and fifty-nine subjects (97.7%) had normal PASP while 11 (2.3%) had elevated PASP. Those with elevated PASP had a significantly higher mean TRV of 2.7 ± 0.22 cm/s (95% CI; 2.55-2.85) *vs* TRV of 1.56 ± 0.43cm/s (95% CI; 1.52-1.60) and higher mean PASP of 39.27±4.89 mmHg (95% CI; 35.99-42.56) *vs* 20.45 ± 5.34 mHg (95% CI; 19.96-20.94) (p=0.001). Though majority of the children had appropriate weight for ages, those with elevated PASP had a significantly greater weight than those with normal PASP (p<0.001). There was a weak positive correlation of PASP with age (r=0.16) and BMI in normal weight (r=0.08). Obese children had a negative correlation value(r=-0.13). A weak negative correlation of PASP with BMI was seen in underweight (r=-0.17 and overweight (r=-0.73) children (p>0.05).

Conclusion: The mean pulmonary artery systolic pressure in the studied apparently healthy Nigerian children was 20.45± 5.34/ mmHg. The frequency of elevated PASP was 2.3%, commoner in children with higher BMI. Age and body mass index are not optimal predictors of PASP.

Key Words: *Pulmonary artery systolic pressure, Children, Pulmonary hypertension, Echocardiography.*

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INTRODUCTION

Pulmonary artery systolic pressure (PASP) represents the pressure exerted within the pulmonary vessels and provides a direct estimation of the right heart pressure.[1] The normal PASP at rest has been generally reported to be much lower than systolic blood pressure due to the large cross- sectional area of the pulmonary vasculature which leads to low resistance.[2] Pulmonary artery systolic pressure measurement is the key to making a diagnosis of pulmonary hypertension which is the fourth most prevalent cardiovascular disease worldwide.[1]

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Echocardiography has been recognized as a reliable method for non-invasive assessment of pulmonary artery pressures because it is simple and safe and has a high cost-benefit ratio.[2-4] In the absence of right ventricular outflow tract obstruction, tricuspid regurgitation velocity measured by Doppler ultrasound can be used to estimate the pulmonary artery systolic pressures.[5,6] In addition, echocardiography enables visualization of the right atrial and ventricular sizes and the inferior vena cava inspiratory collapse which are all essential in accurately measuring pulmonary pressure.[1,5,9] Thus, echocardiography is important for the initial evaluation of pulmonary hypertension prior to right heart catheterization when indicated to confirm the diagnosis of suspected cases.[7,8]

Pulmonary hypertension in children presents initially with subtle signs and symptoms which makes early diagnosis difficult. Thus, affected children present late with complications which usually leads to mortality within a year of diagnosis.[9,10]

Pulmonary hypertension has been noted as the fourth most prevalent cardiovascular disease in the world, though this goes unnoticed by the WHO Global Action Plan and Global Burden of Diseases.[12] Data on global prevalence of pulmonary hypertension is lacking; a well knitted and coordinated action is therefore needed for screening and intervention.[10]

Currently there is a paucity of data on assessment of pulmonary pressure in Nigerian children. A number of children present with late sequel of pulmonary hypertension with unspecific symptoms, which eventually could result in death. Early detection of pulmonary hypertension would help avert such sequel. Ascertaining normative values of pulmonary pressure in Southern Nigerian children will help the clinician to have a good index of suspicion in the management of pulmonary hypertension in children. Hence the aim of this study was to determine the frequency and severity of pulmonary hypertension among apparently healthy children in South Nigeria, as well as the relationship of PASP with age and body mass index (BMI).

METHODOLOGY

The study was carried out from January 2010 to December 2019 in University of Nigeria Teaching Hospital Ituku-Ozalla Enugu, Lagos State University Teaching Hospital, Niger Delta University Teaching Hospital Bayelsa and Blessed Children Hospital Enugu. These institutions which lie in the rain forest zone serve as referral centers for various health institutions in southern Nigeria.

This was an observational and cross-sectional study involving 470 apparently healthy children aged 1 to 17 years who presented to the Paediatric Outpatient clinic of hospitals of study for follow up after recovery from a non-pulmonary, non--cardiovascular mild illnesses. Children who had acute illnesses such as respiratory tract infection, malaria or any chronic illnesses such as haemoglobinopathy, cancer, immunosuppression, and all types of cardiac diseases demonstrated by means of echocardiography were excluded from the study. Informed consent was obtained from parents while children over the age of 7 years gave assent.

Weight was measured in kilograms using a standard weighing scale; while height or supine length (for those less than 2 years) was measured in centimeters using a stadiometer to the nearest 0.1 kg and 0.1cm, respectively. The WHO anthro and anthroplus application were used to calculate the mass index (BMI). Transthoracic echocardiogram was done on each child using an SSI-8000 Sonoscape cardiac ultrasound system, Esaote™ Gamma echocardiography machine, Vivid Q Doppler echocardiography machine, and Agilent 4500 echocardiography machine in the respective institution. For echocardiographic examination, the child was placed in a left lateral decubitus position after a detailed explanation of the procedure. Mild sedative was given to those who were uncooperative.

The inferior vena cava was also visualised in the subcostal view to ensure that it was collapsible to at least 50%.[8] Using 2 D and color Doppler, four major views of the heart were assessed to assess the presence of tricuspid regurgitation and determine the point of maximal velocity. When determined, the maximal jet velocity of the tricuspid regurgitation was measured using continuous wave spectral display.

Using the Bernoulli equation (pressure gradient=4 x peak velocity)[2,8,9] the trans-tricuspid gradient was calculated for each participant. The right atrial pressure (RAP), which is a measure of the central venous pressure, was put at 10mmHg. Pulmonary artery systolic pressure (PASP) was calculated by adding the trans-tricuspid pressure gradient to the estimated RAP. The normal pulmonary artery pressure was determined to be TRV of <2.5mmHg and PASP of ≤35mmHg.[8,9]

Ethical clearance was obtained from all the institutions of study through their various Ethical and review committee before commencement of the study.

The data was analysed using SPSS version 25 software (IBM, USA). Descriptive statistics (mean, standard deviation S.D, frequency and percentage) was used to present the data as appropriate. Chi-square was used to assess the association of PASP with sociodemographic variables. T-test was used to compare the difference in continuous variables as appropriate. Pearson was also used to find the correlation between PASP and BMI. All analysis was done at a 95% confidence interval and a p-value less than 0.05 was considered significant.

RESULTS

A total of 470 children were recruited for the study; 49.4% were males, while 50.6% were females giving a male-to-female ratio of 1:1. Their ages ranged from 1 to 17 years with a mean age of 7.9 ±3.3 years. Majority of the participants (n = 328, 69.8%) were aged 6 to 12 years (Table I): Regarding BMI, 24 (5.1%) children were underweight, 375 (79.8%) were of normal weight, 45 (9.6%) were overweight and 26 (5.5%) were obese.

Of the 470 children studied, 459 (97.7%) had normal pulmonary artery systolic pressures (PASP). Eleven children were found to have elevated PASP, giving a frequency of elevated PASP of 2.3%. The tricuspid regurgitation velocities (TRV) of those with normal pulmonary pressures ranged from 0.63 to 2.45 m/s with a mean TRV of 1.56 ± 0.43/s (95% CI; 1.52-1.60), while their PASP ranged from 11.6 to 34.0 mmHg with a mean PASP of 20.45± 5.34 m Hg (95%CI; 19.96-20.94). For those with elevated PASP, their tricuspid regurgitation velocities ranged from 2.5 to 3.1m/s with a mean TRV of 2.7± 0.22/second (95% CI; 2.55-2.85) while their PASP ranged from 35.0 to 48.4 mmHg with a mean PASP of 39.27± 4.9 mmHg (95% CI; 35.99-42.56).

The mean age and height were similar in children with normal and elevated PASP ($p>0.05$). The children with elevated PASP were significantly heavier than those with normal PASP ($p<0.001$). Table I). Tricuspid regurgitation velocity/gradient and pulmonary artery systolic pressures in children with normal and elevated PASP are also shown in Table I.

Table I: Comparisons of age, weight, height, tricuspid regurgitation velocity/gradient and pulmonary artery systolic pressures in children with normal and elevated PASP

Variables	Normal PASP mean ± SD n=459	Elevated PASP mean ± SD n=11	(p-value)
Age in years	7.8 ±3.3	9.6 ±5.7	(0.073)
Weight (Kg)	26.5 ±11.5	47.3 ±39.0	(0.001)*
Height (cm)	127.0 ±19.9	137.1 ±35.6	(0.101)
Tricuspid regurgitation velocity (m/s)	1.6 ±0.4	2.7 ±0.2	(<0.001)*
Tricuspid pressure gradient (mmHg)	10.5 ±5.3	29.3 ±4.9	(<0.001)*
Pulmonary artery systolic pressures (PASP) mmHg	20.5 ±5.3	39.3 ±4.9	(<0.001)*

**Difference between both groups is statistically significant.*

Table II: Distribution of pulmonary artery sytolic pressures with gender and BMI.

Variables	Normal PASP (n, %)	Elevated PASP (n, %)	
Gender			
Male	225 (49.0)	7 (63.6)	0.92 (0.338)
Female	234 (51.0)	4 (36.4)	
BMI			
Underweight	399 (86.9)	6 (54.5)	
Normal weight	49 (10.7)	3 (27.3)	17.70 (0.001)*
Overweight	3 (0.7)	0 (0.0)	
Obese	8 (1.7)	2 (18.2)	
Total	459 (100%)	11(100%)	

**Statistical significance (p <0.05).*

Majority of the children with normal PASP were of normal weight (n=372, 81.0%) while most of the children with elevated PASP were obese (n=5, 45.4%) and this was statistically significant (p=0.001). There was however no difference in pulmonary artery systolic pressures between the male and female children (p=0.338, Table II).

There was a weak positive correlation of PASP and BMI in children with normal weight (r=0.08, p=0.552) and in obese children (r= -0.13, p=0.718). There was a weak negative correlation between PASP and BMI in overweight children (r=-0.73,p=0.483) and a strong negative correlation between PASP and BMI in underweight children (r = -0.17, p=0.001).

DISCUSSION

Echocardiographic evaluation of pulmonary pressures has been widely adopted for non-invasive screening of pulmonary arterial hypertension (PAH) in children.[7,10] It is a readily available and safe procedure which gives an accurate estimation of the status of the right heart and forms the baseline for further invasive investigations.[1,10] In this study, majority of the children (97.7%) had normal pulmonary artery systolic pressures with a mean pressure of 20.45 ± 5.34 mmHg. This finding corroborates with the normal PASP values at rest of 18 to 25mmHg found in literature.[2] Elevated PASP in children without underlying cardiac and respiratory diseases has been found to be rare. When present, it is assumed to be idiopathic or familial in etiology. Several studies have also shown increased risk in children with associated chromosomal abnormalities, especially trisomy.[11,12]

Elevated PASP was found in 2.3% of the children in our study which is similar to that seen in other studies.[5,13] In previous studies on pulmonary hypertension in children, the incidence of idiopathic PAH has been reported to range from 0.47 to 2.1 cases per million children per year with prevalence rates of 2.1-4.4 cases per million children per year.[10,13,14] It is possible that these lower rates were due to the fact that these studies involved children without any underlying medical condition. This assertion is buttressed by the fact that the prevalence of elevated PAH is more in children with uncorrected congenital heart disease and other chronic medical conditions.[15,16-18]

There were no significant age or gender differences in children with normal or elevated PASP in this study. Nevertheless, among children with elevated PASP, a slight female preponderance was observed. This is similar to reports by other authors who also noted a female preponderance in children with elevated pulmonary pressures.[2,16-18] Genetic factors have been described as an important underlying cause of elevated pulmonary arterial pressure as a genetic mutation in the bone morphogenetic protein 2 (BMPR2) gene has been linked to pulmonary arterial hypertension.[19,20] Females have a higher tendency of elaborating this mutation in the BMPR2 receptor compared to males, which could explain this female predominance.[21-23]

The mean age of 9.6 ±5.7 years among children with elevated PASP in the present study was higher than the average age of 7 years reported by some authors.[20,22] Changes in pulmonary pressures have been shown to be independent of race or gender but could be influenced by age.[1,22] This is corroborated by the fact that there is a lower

prevalence of idiopathic PAH in children compared to adults.[13] These increases in pulmonary arterial pressure with age can be explained by decreasing trans-pulmonary blood flow and increase in systemic pulse pressure that occur with increasing age. In addition, the increase in intimal proliferation and thickening with age can lead to an increase in pulmonary arterial pressure.[23-25]

In this study, there was a weak positive correlation of PASP with age and BMI in normal weight and obese children. This shows that age and BMI are sub-optimal predictors of pulmonary artery systolic pressure.

This study has helped in establishing baseline values of pulmonary pressure among Southern Nigerian children. The values will assist the physician in suspecting an impending danger when the normal levels are exceeded. Since the prevalence of elevated PASP in Nigerian children is commoner in heavier children, a rigorous dietary manipulation and health education is necessary to avert the numerous complications associated with overweight and obesity.

CONCLUSION

The prevalence of elevated PASP in normal Nigerian children is low and is commoner in children with greater weight. Age and body mass index are not an optimal predictor of PASP. The mean pulmonary artery systolic pressures in apparently healthy Nigerian children is 20.45± 5.34 mmHg.

ETHICAL APPROVAL: Prior to the initiation of this work, ethical approvals were obtained from the Ethics and Research Committee of the University of Nigeria Teaching Hospital, Enugu (IRB No. 00002323), Lagos State University Teaching Hospital (IRB No. LREC/10/06/317) and Niger Delta University Teaching Hospital, Bayelsa (IRB No. NDUTH/REC/2019/0038).

PATIENTS' CONSENT:
Informed consents were granted by the parents/caregivers of the subjects.

CONFLICT OF INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
COD, JMC, PAU, MOL: Contributed to the conception, writing and proofreading of this manuscript. All authors read and approved the final manuscript.

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