International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 13-08-2020; Accepted: 28-08-2020; Published: 14-09-2020
www.medicalsciencejournal.com
Volume 6; Issue 9; 2020; Page No. 39-44

Pulmonary artery pressure and right heart linear dimensions in Nigerian children with sickle cell anaemia

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Abstract

Background: Pulmonary hypertension (PH) is a long-term complication of sickle cell anaemia (SCA). The most obvious pathophysiologic consequence of PH is on the right heart, causing right ventricular and right atrial dilatation with subsequent right heart failure. Progressive dilatation of the right atrium and right ventricle, makes echocardiographic evaluation of right heart linear dimensions important in the evaluation of patients with PH.

Aim: To assess possible relationship between mean pulmonary artery pressure and right heart linear dimensions.

Methods: This was a cross-sectional study involving children with SCA aged 6 months -15 years. The study was conducted from September 1st 2013 to 30th August 2015, at the SCA clinic of the Department of Paediatrics, Usmanu Danfodiyo University Teaching Hospital, Sokoto. North-Western Nigeria.

Result: Three hundred children with SCA in steady state were enrolled in to the study. The age range of the children was 6 months – 15 years, with mean age of 6.5 ± 4.1 years. Subjects were grouped in to three, group one comprises of children with normal pulmonary artery pressure (PAP) defined as peak tricuspid regurgitant velocity (TRV) of ≤ 2.5m/s and mean pulmonary pressure (MPAP) of < 25 mmHg; group two comprises of children with elevated PAP, defined as TRV ≥ 2.5 m/s and MPAP of < 25 mmHg; and group 3 comprises of children with PH, defined as mean pulmonary artery pressure (MPAP) ≥25 mmHg. The mean values in millimetre of the right atrial (RA) major axis (34.5 ± 5.6 vs 31.2 ± 8.6, p <0.001), RA minor axis (30.2 ± 6.1 vs 25.8 ± 6.7, p < 0.001), right ventricular (RV) basal diameter (33.0 ± 15.8 vs 26.0 ± 9.4, p = 0.01), RV mid-cavity diameter (35.9 ± 6.9 vs 21.8 ± 8.9, p < 0.001) and RV longitudinal diameter (56.7 ± 11.4 vs 45.2 ± 16.1, p < 0.001) were significantly higher in patients with elevated PAP compared to those with normal PAP. RA minor axis, RA major axis, RV mid-cavity diameter and RV longitudinal diameter independently varies with mean pulmonary artery pressure (MPAP), with 86% (44% of 51%) of the variability accounted for by the RA minor axis alone.

Conclusion: Right heart linear dimensions have significant association with MPAP, and can be of use in the echocardiographic evaluation of PH among children with SCA.

Keywords: right heart linear dimensions, pulmonary artery pressure, sickle cell anaemia

Introduction

Sickle cell anaemia is a genetic disorder with multi systemic consequences, including significant haemodynamic effect on the cardiovascular system. The earliest description of the condition by Herrick included cardiac enlargement and a precordial murmur in his patient [1]. Yater and Hansmann gave the first detailed description of the pulmonary complications of SCA in form of pulmonary hypertension and right heart failure [2].

An estimate of around 20-25 million individuals worldwide have SCA, of which 12-15 million live in sub-Saharan Africa [3, 4]. Nigeria has the highest burden of SCA worldwide with a prevalence of 20 per 1000 live births annually [5]. Higher prevalence of 4.75% [6], was reported in the study area from a Hospital based study.

Haemolysis and vaso-occlusion are the hallmark of clinical manifestation of SCA, resulting to vaso-occlusive pain crises, anaemia, dactylitis or hand-foot syndrome, splenic sequestration, acute chest syndrome, priapism in male patients, delayed growth and puberty, leg ulcers among others. With increasing age, SCA is associated with chronic end-organ complications such as chronic renal failure, haemorrhagic and non-haemorrhagic stroke, avascular necrosis of bone and PH [7, 8].

PH is becoming one of the leading causes of death in young adults with SCA both in developed and developing countries [7, 9]. Prevalence of 20-40% has been reported among adult patients with SCA [10, 13], and autopsy studies have suggested that up to 75% of adult patients with SCA have histological evidence of pulmonary hypertension at the time of death [14]. The condition confers a high risk of death in SCA patients with 2-year mortality rates of 40–50%, even at modest elevations of pulmonary pressures [7, 15].

In the presence of PH, there is progressive dilatation of the right heart chambers [16]. Right ventricular pressure rises gradually and pulmonary pressure may exceed the systemic pressure. Decrease in cardiac output occurs as a result of impaired cardiac function from RV volume and pressure overload, primarily by impairing coronary perfusion of the hypertrophied and dilated RV [17], leading to right heart failure. Raymond *et al* [18], had previously shown that RA size measured with echocardiography was of prognostic significance in patients with idiopathic PH. Echocardiographic assessment of PH includes detection of elevated PAP values and functional evaluation of the right heart [19].

This study aimed at evaluate the relationship between right heart linear dimensions (right atrial minor and major axis, right ventricular basal, mid-cavity and longitudinal diameters) and mean pulmonary artery pressure in children with SCA.

Materials, Subjects and Methods

This was a cross-sectional study carried out at the sickle cell clinic of the Department of Paediatrics, Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto, Sokoto state North-Western Nigeria. Children aged 6 months to 15 years with the diagnosis of SCA in steady state, who were on follow up at the sickle cell clinic of the Department of Paediatrics, were recruited in to the study after informed written consent, and assent where necessary, were obtained. Steady state in this study was defined as absence of painful crisis, blood transfusion, acute clinical symptoms, crisis, or febrile illness warranting hospitalisation in the preceding three months.

Children that fulfilled the following inclusion criteria were recruited for the study

1. Age 6 months to 15 years.
2. Hb Electrophoretic pattern SS
3. Absence of crisis, inter current illness such as bronchopneumonia, asthma or any illness that warranted hospitalisation or blood transfusion in the preceding three months

Subjects with the following conditions were excluded from the study

1. Presence of chest wall deformities.
2. Patients on therapies known to have effect on pulmonary artery pressure such as anorectic agents, hydroxyurea or chronic transfusion therapy.
3. Presence of functional or structural abnormality of the heart or great vessels, like systolic dysfunction, congenital abnormalities of the heart and the great vessels including branch pulmonary stenosis.
4. Presence of obvious clinical symptoms of cardiac involvement by infectious, neuromuscular or metabolic disorder; or clinical symptoms of lung disease, asthma, adenoidal hypertrophy, kidney or connective tissue disease and fever.
5. Absence of measurable tricuspid regurgitation jet

Recruited children were selected by simple random sampling, using a table of random digits according to the way they were numbered in the outpatient register for the day. Ethical approval for the study was obtained from the Hospital ethics Committee.

All the children were subjected to clinical evaluation. Relevant clinical history including age, age at diagnosis of SCA, medications, and presence or history of chronic complications were recorded. Each patient had general physical examination including measurement of anthropometric indices, body mass index (BMI), body surface area (BSA) and clinical assessment for pallor, jaundice and central cyanosis. Anthropometric measurements were performed according to standard procedures of the World Health Organisation [20]. Length/height were taken to the nearest 0.01 cm. BMI and BSA were calculated manually using Quetelet index {BMI = Weight (Kg)/Height^2 (M)} [21], and Mosteller formula {√weight (kg) x height (cm)/3600} [22] respectively.

Cardiovascular examination was conducted. Blood pressures were taken in accordance with the Working group of the National High Blood Pressure Education program (NHBPEP, 2004) [17]. Heart sounds were regarded as normal when the first heart sound is single and louder at the apex with normally split-second heart sound in inspiration appreciable at the second left intercostal space [23].

Standard two-dimensional and Doppler echocardiography was performed in the supine and left lateral decubitus positions using SSI-5000 Sonoscape echocardiography machine (SonoscapeYizhe Building, Yuquan Road, Shenzhen China) with a 3.5–7 MHz transducer. Standard parasternal long and short axes, apical, subcostal, and suprasternal views were used. Screening echocardiography was done first to rule out structural heart abnormalities including right ventricular out flow and branch pulmonary artery obstruction. Left ventricular systolic function was assessed by calculating left ventricular ejection fraction using Simpson's rule. Subjects with ejection fraction greater than 54% - 75% were regarded to have normal left ventricular systolic function [24]. From apical 4-chamber view, RV focused view was obtained and RA major axis and minor axis dimensions as well as RV basal, mid cavity and longitudinal diameters were measured as shown in figure 1 & 2 below:

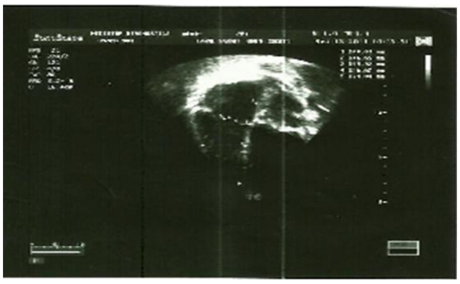

Fig 1: Right heart linear dimensions (RA major & RA minor axes) of a 4-year-old girl with SCA from the study patients measured from apical 4 chamber view (RV focused view).

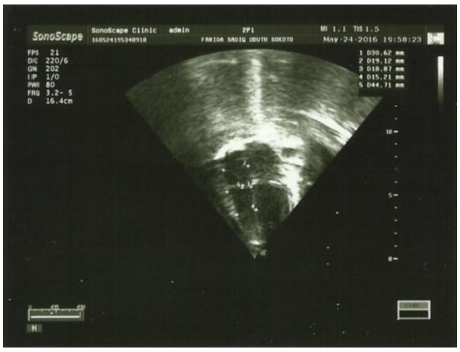

Fig 2: Right heart linear dimensions from "RV focused view" in 18 months old HbAA girl. RA minor is 19.1 mm, RA major axis 30.7 mm, RV basal diameter 18.9 mm, RV mid-cavity diameter 15.2 mm, and RV longitudinal diameter of 44.7 mm

Colour Doppler interrogation was used to detect tricuspid regurgitation from the apical 4-chamber, RV inflow, parasternal short axis and subcostal views. Tricuspid valve morphology was assessed to ensure normal tricuspid valve morphology. Tricuspid regurgitant jet velocity (TRV) was recorded and the maximum value obtained was taken as the peak velocity. Mean gradient (MG)) was measured by continuous wave Doppler using area under the curve method as shown in figures 3 and 4 below:

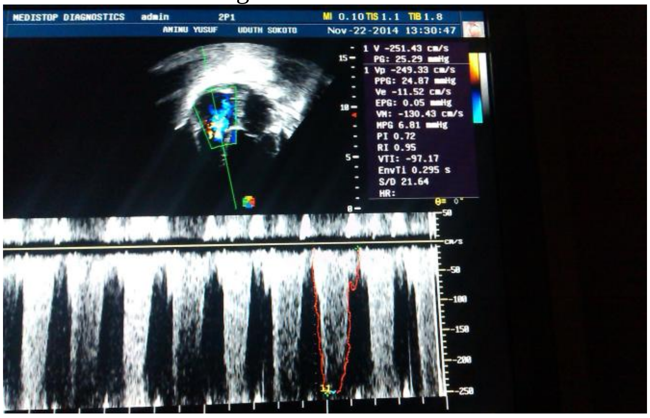

Fig 3: Colour flow Doppler with area under the curve mapping in an 8-year-old boy with SCA. The patient had elevated PAP with peak TRV of 2.51 m/s and the MG of 6.8 mmHg.

Pressure gradient (ΔP) between the right ventricle and the right atrium was calculated using the Bernoulli equation:

P_1-P_2 (ΔP) = $4V^2$

Where P_1 is the right ventricular pressure, P_2 is the right atrial pressure and V the peak TR velocity. Ten per cent of ΔP was taken as estimated right atrial pressure [25]. This was added to the mean gradient (MG) derived from the area under the curve to get the MPAP (see figure 4).

MPAP = MG + RAP (10% of $4TRV^2$). PASP was estimated using modified Bernoulli equation as follow:

PASP = ($4xTRV^2$) + estimated right atrial pressure (10% of ΔP) [25].

Fig 4: Colour flow Doppler with area under the curve mapping in a 5-year-old girl with SCA and pulmonary hypertension. The peak TRV was 3.6 m/s while the mean gradient (MG) was 23.3 mmHg. Estimated RPA was 5 mmHg (10% of $4TRV^2$). The MPAP was 28 mmHg (MG + RPA).

For the evaluation of the relationship between the right heart dimensions and the pulmonary artery pressure in children with SCA, patients were grouped in to three based on TRV and MPAP; group 1 comprises of patients with TRV < 2.5 m/s and MPAP < 25 mmHg constituting the normal PAP group, group 2 comprises of patients with TRV ≥ 2.5 m/s and MPAP < 25 mmHg constituting the elevated PAP group, and group 3 comprises of patients with TRV ≥ to 2.5 m/s and MPAP ≥ to 25 mmHg and they constituted the PH group.

Quality Assurance: All echocardiographic measurements were done according to the recommendations of the American Society of Echocardiography [26]. The arithmetic mean of three consecutive measurements were used. All images and measurements were recorded and reviewed by at least 2 of the 3 Consultant Paediatric Cardiologists. The TR jet was interrogated from multiple different views (RV inflow, apical four chamber, parasternal short axis and subcostal views) to ensure that the ultrasound beam is parallel to the regurgitant signal, thus allowing optimal Doppler envelope quality and an accurate peak trans tricuspid flow velocity (TTFV) [26]. The apical 4-chamber view was adjusted from its usual attention on the left ventricle to a focus on the right ventricle to acquire the ‘‘right ventricle–focused view’’ when measuring the right heart dimensions [26].

Data analysis: Obtained data was analysed using the Statistical Program for Social Science (SPSS) version 20.0 for windows. Continuous variables were summarised as means and standard deviations and categorical variables as frequencies and percentages. Mean values were compared between two groups by independent sample t-test while frequencies and percentages between two groups were compared using Chi-square or Fisher’s exact test where figures are small.

In evaluating the relationship between the right heart dimensions and pulmonary artery pressure, mean TRV; MPAP; and right heart dimensions were compared between the three groups based on TRV and MPAP value as earlier explained, using one-way ANOVA. Standard multiple regression models were used to assess the relationship of sets of right heart variables with MPAP, and stepwise multiple regression (forward) models were used to assess independent variability of MPAP with the set of the right heart linear dimensions. A p-value < 0.05 was considered statistically significant at 95% CI.

Results

Demographic characteristics

The age range of the studied children was 0.5- 15 years, with mean age of 6.5 ± 4.1 years. One hundred and fifty-six (52.0%) were males and 144 were females with M: F of 1.1:1.

Pattern of PAP in the study population

Seventy two out of the 300 (24.0%) patients with SCA had elevated PAP defined as TRV of ≥ 2.5 m/s. None of the children studied aged less than 1 year had elevated PAP. The range of MPAP values in children with SCA was 2.0 – 35.0 with mean of 10.2 ± 5.8. Nine children (3.0%) had MPAP ≥ 25 mmHg indicative of PH.

Right heart linear dimensions and pulmonary artery pressure in children with SCA.

For evaluating the relationship between mean pulmonary artery pressure and right heart linear dimensions, children with SCA were grouped in to three as earlier highlighted. Mean echocardiographic parameters were compared between the three groups using one-way ANOVA, as shown in Table I. There were statistically significant difference among the three groups in the mean RA major axis [$F(2,297) = 28.89$, $p < 0.001$], RA minor axis [$F(2,297) = 50.33$, $p < 0.001$], RV basal diameter [$F(2,297) = 10.82$, $p < 0.001$], RV mid-cavity diameter [$F(2,297) = 24.04$, $p < 0.001$] and RV longitudinal diameter [$F(2,297) = 38.62$, $p < 0.001$].

Table 1: Comparison of the echocardiographic parameters of patients with SCA according to Pulmonary Artery Pressure group

Parameter	Normal PAP N = 228	Elevated PAP N = 63	PH N = 9
TRV, m/s (mean±SD)	1.7 ± 0.4	2.9 ± 0.3	3.6 ± 0.4
MPAP, mmHg (mean±SD)	7.7 ± 3.2	18.0 ± 5.2	27.9 ± 3.1
RA major axis, mm (mean±SD)	33.3 ± 4.9	38.8 ±5.1	36.2 ± 7.7
RA minor axis, mm (mean±SD)	28.6 ± 5.5	34.5 ± 4.8	40.8 ± 2.9
RV basal diameter, mm (mean±SD)	30.7 ± 6.4	40.5 ± 31.3	38.8 ± 5.0
RV mid-cavity diameter, mm (mean±SD)	34.5± 6.2	40.7 ± 6.9	39.6 ± 9.5
RV longitudinal diameter, mm (mean±SD)	53.9 ± 9.9	65.1 ± 11.1	70.3 ± 6.9

Mean RA major axis was significantly higher in the group with elevated PAP (38.8 mm ± 5.1, p<0.001) than in those with normal PAP (33.3±4.9 mm). It was also higher in the group with PH (36.2 mm vs 33.3 mm) compared to those with normal PAP, but the difference was not significant (p = 0.20). Mean RA major axis was lower in the PH group (36.2 ± 7.7 mm) compared to the group with elevated PAP (38.8 ± 5.2 mm) but the difference was not statistically significant (p = 0.35). The mean RA minor axis was significantly higher in the group with elevated PAP (34.5 ± 4.8 mm, p <0.001) and PH group (40.8 ± 2.9 mm, p< 0.001) compared to the group with normal PAP (28.6 ± 5.5 mm). Mean RA minor axis was also significantly higher in the group with PH (40.8 ± 2.9 mm, p = 0.003) compared to the elevated PAP group (34.5 ± 4.8 mm).

Mean RV basal diameter was significantly higher in patients with elevated PAP (40.5 ± 31.3 mm, p<0.001) compared to patients with normal PAP (30.7 ± 6.4 mm). Even though the mean RV basal diameter was higher in patients with PH (38.8 ± 5.0 mm) compared to patients with normal PAP (30.7 ± 6.4 mm), the difference was not statistically significant (p = 0.27). The mean RV basal diameter was lower in patients with PH (38.8 ± 5.0 mm) compared to those with elevated PAP (40.5 ± 31.1 mm), but the difference was not statistically significant (p = 0.95).

Mean RV mid-cavity diameter was significantly higher in patients with elevated PAP (40.7 ± 6.9 mm) compared to patients with normal PAP (34.5 ± 6.2 mm, p<0.001). Mean RV mid-cavity diameter was higher in patients with PH (39.6 ± 9.5 mm) compared to those with normal PAP (34.5 ± 6.2 mm), but the difference was not statistically significant (p = 0.05). Mean RV mid-cavity diameter was lower in patients with PH (39.6 ± 9.5 mm) compared to those with elevated PAP (40.7 mm ± 6.9), but the difference was not statistically significant (p = 0.89).

Mean RV longitudinal dimension was significantly higher in patients with elevated PAP (65.1 ± 11.1 mm, p <0.001) and patients with PH (70.3 ± 6.9 mm, p<0.001) compared to patients with normal PAP (53.9 ± 9.9 mm). Patients with PH equally had higher mean RV longitudinal dimension (70.3 ± 6.9 mm) compared to those with elevated PAP (65.1 ± 11.1 mm), but the difference was not statistically significant (p = 0.33).

The change in mean of the individual right heart linear dimensions within the PAP groups was not uniform. While the mean of all the right heart dimensions were higher in patients with elevated PAP compared to those with normal PAP, that was not the case when right heart linear dimensions were compared between patients with elevated PAP and those with PH. Mean RA minor axis was higher than the mean RA major axis in patients with PH as depicted in table I above, and that only mean RA minor axis and RV longitudinal dimension were progressively increasing from normal PAP group through the elevated PAP group to the PH group.

Multiple regression model for the relationship of MPAP with right heart linear dimensions:

Variation of MPAP with the set of right heart dimensions; RA minor axis, RA major axis, RV basal diameter, RV mid-cavity diameter and RV longitudinal dimension was assessed using standard multiple regression. The covariates of RA minor axis, RA major axis, RV mid-cavity diameter and RV longitudinal dimension significantly varies with MPAP as shown in Table II. The multiple correlation coefficient was 0.72 and the combined variability was 51% (R^2 = 0.51). Unlike other right heart dimensions above, no significant variation was found between the RV basal diameter and MPAP (p = 0.41).

Table 2: Variability of MPAP with right heart linear dimensions

Right heart dimensions	Pearson r	β coefficient	95% CI	P
RA minor axis	0.66	0.97	0 .72 - 1.13	<0.001
RA major axis	0.46	-0.45	-0.62 - -0.27	<0.001
RV basal diameter	0.26	0.01	-0.02 - 0.05	0.41
RV mid-cavity diameter	0.46	-0.25	-0.34 - -0.07	0.003
RV longitudinal diameter	0.60	0.29	0.04 - 0.26	0 .01

R^2 = 0.51, C = -3.52, C is the regression Constant

The final regression equation relating MPAP with a set of right heart linear dimensions was derived as follows

MPAP = 0.97 x Ramn + 0.29 x RVlon – 0.45 x RAmj – 0.25 x RVmc – 3.52

Where:

Ramn is RA minor axis

RVlon is the RV longitudinal diameter

RAmj is the RA major axis

RVmc is the RV mid-cavity diameter

The individual digits for each right heart linear dimension in the derived equation represents, the regression coefficient (β-coefficient from table II above) of the corresponding right heart linear dimension.

Stepwise multiple regression models (Forward) were further employed to quantify independent variability of MPAP with each right heart linear dimension found to be independently varied with MPAP, from multiple regressions above, see table III.

Table 3: Stepwise multiple regression result of the right heart dimensions and MPAP

Right heart dimensions	R	R^2	95% CI	P
RA minor axis	0.66	0.44	0.72 - 1.13	<0.001
RA major axis	0.70	0.49	-0.62 - -0.27	<0.001
RV mid-cavity diameter	0.71	0.50	-0.34 - -0.07	0.003
RV longitudinal diameter	0.71	0.51	0.04 – 0.26	0.01

Constant = -3.52

The result shows that, the major variability of the MPAP with right heart linear dimensions was accounted for by RA minor axis (44% out of 51%), followed by the RA major axis (5% out of 51%), followed by RV mid-cavity and RV longitudinal diameters (1% each of the 51%).

Discussion

The role of echocardiography in the evaluation of pulmonary hypertension cannot be over emphasized, especially in patients with SCA. Most of the studies in the past focused on adult patients, with paucity of data in children with SCA especially from the Sub-Saharan Africa.

Dilatation of the right chambers of the heart is an established consequence of longstanding PH [27]. This could explain why the mean of all the five right heart linear dimensions measured in this study were significantly higher in patients with elevated PAP and PH than in those with normal PAP, and justify the inclusion of the functional evaluation of the right heart including right heart linear dimensions in the echocardiographic evaluation of patients with PH [19].

This study identified significant association between right heart linear dimensions and MPAP in the largest cross-sectional series of children with SCA in Nigeria. Raymond *et al* [18], reported that RA size measured by indexed right atrial area was an independent predictor of the composite endpoint of death or transplantation in adults with primary PH. It has also been proven to be a prognostic marker for follow up of patients with PH both adults and children [18, 27]. Right atrial area was also reported to be predictive of outcome in patients with Eisenmenger syndrome [28].

Considering the fact that RA area is a product of RA minor and major axes, this is in support of the significant variability between RA minor axis and RA major axis with MPAP in this study. Perhaps RA minor axis being the major contributor to the association between the two RA linear dimensions combined and PH.

The findings of higher mean RV linear dimensions among patients with elevated PAP and PH, when compared to those with normal PAP in this study is in conformity with progressive hypertrophy and dilatation of the right ventricle in patients with PH. RV dilatation has been reported to be an early sign of RV dysfunction [29], and indexed RV basal diameter have been associated with poor prognosis in adult patients with chronic pulmonary disease [30]. Similar findings were also reported in children with PH, although the measurements of RV end diastolic dimensions were measured from the parasternal short axis view, from M-mode [31]. In another study by McLean *et al* [32], RV mid-cavity diameter was significantly high in adult patients with PH, and a cut-off value of 36.0 cm significantly predicted the presence of PH.

It is worthy of note that in this study, although all the mean right heart linear dimensions evaluated were higher in patients with elevated PAP than in those with normal PAP, the mean RA major axis, RV basal diameter and RV mid-cavity diameter were lower in patients with PH compared to patients with elevated PAP alone. Only mean RA minor axis and RV longitudinal diameter were higher in patients with PH, when compared to those with elevated PAP without PH. This indicates that not all the right heart linear dimensions continue to increase with progressive increase in MPAP in the face of PH. This explains the variation in the degree of association between the right heart linear dimensions and the MPAP noticed in this study. Perhaps that is why RA minor axis and RV longitudinal diameter has more significant positive association with the MPAP, and the RV basal diameter eventually becomes eliminated in the final equation.

Conclusion

There is significant relationship between right heart linear dimensions and mean pulmonary artery pressure. Right atrial minor and major axes, right ventricular mid-cavity diameter and right ventricular longitudinal diameter had significant relationship with MPAP. Right atrial minor axis has the potential for use in the echocardiographic evaluation of patients with PH, as it is associated with major variability with MPAP. There is need for multi-centred research on the relationship between right heart linear dimensions and PAP to further strengthened the findings in this study and justify including right heart dimensions assessment as part of the echocardiographic evaluation of children with PH.

Acknowledgements

The authors appreciate the support and contribution of the health information officers, and staff nurses working at the SCA clinic of the Department of paediatrics in the recruitment of subjects and data collection.

Conflicts of interest

There are no conflicts of interest

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