ORIGINAL ARTICLE

BRONCHIECTASIS IN CHILDREN WITH PRIMARY CILIARY DYSKINESIA: MAIN PULMONARY ARTERY TO ASCENDING AORTA RATIO AS MARKERS OF DISEASE SEVERITY

Adnan Zafar[1], Muhammad Salman Qureshi[2], Saba Ayub[3]✉

[1]Pediatric Department, John Hopkins Aramco Healthcare, Dhahran-Saudi Arabia
[2]King Fahad Medical City, Children Specialized Hospital, Riyadh-Saudi Arabia
[3]Freelancer

Background: Lung function in primary ciliary dyskinesia becomes abnormal from an early age and doing any lung function test in the first few years of life requires a child's cooperation which can be difficult. High Resolution Computed Topography (HRCT) is done every few years to monitor lung structure. We aimed to look at the relationship of bronchiectasis with the size of MPA (main pulmonary artery) and MPA-to-AA (ascending aorta) ratio. This can be used as an additional disease marker when assessing CT chest. **Methods:** This was a retrospective analysis of CT chest measurements in children with confirmed Primary Ciliary Dyskinesia (PCD), followed up at our centre between 2008-2020. Diameters of the main pulmonary artery, ascending and descending aorta were measured at predetermined reference points. The scans were independently analysed by two radiologists. CT chest contrast images were obtained on a 64 slice- Discovery CT750 HD, GE Healthcare medical system. Bronchiectasis was graded using the Modified Reiff scoring method. **Results:** 38 measurements from 26 patients were taken into consideration to assess the relationship between MPA diameter, MPA: Ascending aorta and bronchiectasis**.** There was a positive correlation between the age-adjusted MPA-to-AA ratio and severe bronchiectasis (r=0.59, *p*=0.47). Children without bronchiectasis had an inverse correlation with MPA-to-AA ratio (r= -0.28, p=0.16). MPA diameter was positively related to both severe (r=0.59, *p*=0.06) and no bronchiectasis (r=0.91, *p*=0.01). There was a disproportionate age-dependent increase in the size of MPA in children who had multiple scans once bronchiectasis progressed from mild to severe. **Conclusions:** This is a pioneer study looking at CT chest markers like MPA (diameter) and MPA-to-AA ratio in children with PCD and their relevance to the severity of bronchiectasis. An elevated MPA-to-AA (Ascending Aorta) ratio can be used as a marker of severe bronchiectasis however MPA diameter on its own has limited value in differentiating mild from severe bronchiectasis.

Keywords: Primary ciliary dyskinesial; Bronchiectasis; Main pulmonary artery; Ascending aorta; Bronchiectasis

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INTRODUCTION

Primary ciliary dyskinesia (PCD) commonly presents with recurrent ear, sinus, and chest infections. The global prevalence has been estimated as approximately 1 in 7500 individuals.[1] The reported prevalence is different in different parts of the world due to disparity in access to diagnostic services. Respiratory system involvement starts from the neonatal period but the diagnosis is often delayed due to a lack of awareness of disease presentation and poor access to specialised diagnostic laboratories.[2] Lung function assessment is a well-established predictor of morbidity and mortality in chronic lung disease in children.[3] Monitoring lung function in the early years is difficult due to poor technique in the preschool age group. The decline in lung function starts early in life but accelerates from the age of ten years and above. Spirometry is commonly used in children five years or older who have the correct technique to perform the test.[4] It has low sensitivity to detect early lung damage when compared to high-resolution chest CT.[5] Previous studies reported that approximately 65% of children under the age of five years reliably perform spirometry.[6] Forced expiratory volume in 1 second (FEV1) is the most commonly affected parameter which becomes abnormal between the age of 6 and 11 years.[3,7] The largest registry data for Primary Ciliary Dyskinesia (iPCD Cohort study) reported that a decline in FEV1 starts early in life similar to cystic fibrosis.[8] Poor sensitivity of spirometry to detect the progression of lung disease in PCD may give clinicians a false sense of security in the presence of a stable FEV1.[9]

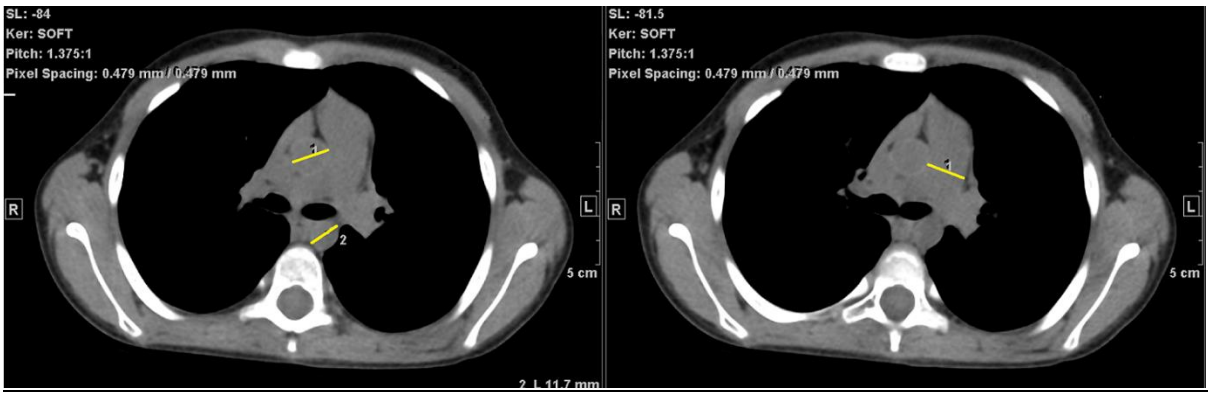
Other techniques like MBW (multiple breath washout) and IOS (impulse oscillometry) are still in the early phase of incorporation into paediatric practice. These tests are performed in very few centres across the world.[10] CPET (cardiopulmonary exercise testing) has been utilised to evaluate lung health in children with chronic lung disease. Parameters like VO2max or VO2 peak can be used to monitor disease progression in PCD. Robinson *et al* did a comprehensive review of CT chest in children with PCD and supported its use to detect early disease.[11] Common CT chest findings in PCD include peribronchial thickening, atelectasis, ground glass opacity and air trapping; progression of these abnormalities leads to bronchiectasis.[12] The upper lobes are mostly spared in PCD. Younger children are sedated and delivered controlled breathing to acquire good quality images[13]. We aimed to look at the usefulness of specific HRCT (High resolution CT) measurements, i.e., Main pulmonary artery diameter, MPA-to-AA ratio, and their correlation with the severity of bronchiectasis. Our other objective was to see if these measurements can be associated with the presence of pulmonary hypertension.

MATERIAL AND METHODS

This was a retrospective single-centre observational study conducted between 2018 and 2020. The study was approved by the local IRB committee.

All children attending King Fahad Medical City multidisciplinary PCD clinic, who had chest CT as part of their clinical evaluation between the years 2008 to 2020, were included in the study. They were aged 0–14 years with a confirmed diagnosis of PCD by genetic testing and nasal brush biopsy. The decision to perform a CT scan was determined on an individual basis by a paediatric respiratory consultant with expertise in PCD. All children with cardiac anomalies other than situs inversus were excluded from the study. These scans were done during the period of clinical stability.

CT images were randomly allocated to two radiologists (DS and MU). Both independently scored CT findings. The severity of bronchiectasis was graded using Modified Reiff score.[14] Quantification was done considering radiological findings in all lung lobes. The following scores were allocated for bronchial dilatation relative to the adjacent pulmonary arteries: 0 = none; 1 = 100–200% arterial diameter; 2 = 200–300% arterial diameter; 3 = >300% arterial diameter, with a maximum score of 18[15]. Ascending Aorta (AA), Descending Aorta (DA) and main pulmonary artery (MPA) diameter were measured using maximum linear measurement. The MPA was measured at its widest point perpendicular to its long axis, excluding its immediate post valvular segment. AA and DA diameter were measured at the level of the right pulmonary artery. Please see the reference image for reference measurement points. (CT image)



CT Image

CT chest contrast images were obtained on a 64 slice-Discovery CT750 HD, GE Healthcare medical system. All our examinations followed the internationally recognised principle of radiation safety, i.e., ALARA (As low as reasonably possible). No studies were ECG-gated. According to our institution's protocol, we used the following imaging parameters based on patient weight: KVp ranges from 80–120, and tube current was selected using a dose modulated technique (Auto mA), volumetric CT dose index ranges from 2.6–4.0 mGy for patients 0–2 years; 3.0–4.5 mGy for 2–5 years; 4–6 mGy for 5–14 years. Field of view was variable and depends on the size of the patient, acquisition slice thickness of 0.625 mm with 1mm reconstructions using a standard reconstruction algorithm. A Pitch of 1.375 and rotation time of 0.5 seconds was used. All the examinations were independently reviewed on standard Centricity Picture

Archiving and Communication System Radiology RA1000, GE Healthcare workstation. In more than 90% of the patients, 2.5 mm axial CT slice thickness was used for the measurement using a window width of 342 HU and a level of 56 HU.

Minitab 19 was used for statistical analysis. Data were expressed as continuous variables using mean values and standard deviation. Paired t-test was used to compare continuous variables of normal and non-normal distribution. We used the Pearson coefficient to show a correlation between variables. The relationship between a response, i.e., bronchiectasis and predictors i.e., MPA size, and MPA-to-AA ratio, was assessed using linear regression with the best-fitted model. All factors were adjusted for age and gender. A 2-sided alpha of less than 0.05 was considered statistically significant

RESULTS

Twenty-six children (F=19, M=7) with a confirmed diagnosis of PCD were included in the study (Table-1). We used ATS guidelines to diagnose PCD. A total of 38 readings were obtained as some patients had multiple scans. The median age of our cohort was 10.9 years. The median age at the scan was 8 years. This was largely dependent on the age at which the child was referred to our centre. The average height was 132cm. The mean MPA diameter and MPA-to-AA ratios were 17.15mm (SD±3.55mm) and 0.97(SD±0.1) respectively. Our study included seven children with situs inversus. None of our patients had pulmonary hypertension on transthoracic ECHO. Nineteen patients (19/26) had bronchiectasis on HRCT. Of these, 73.6% (14/19) had mild while 26.3% (5/19) had severe bronchiectasis. 6/7(86%) of children with situs inversus had bronchiectasis; none of them had severe bronchiectasis.

We analysed the association of age-adjusted MPA and MPA-to-AA ratio with the severity of bronchiectasis (Table-2). Children with severe bronchiectasis had a strong positive correlation with MPA size (r=0.59, p=0.06) and MPA-to-AA ratio (r=0.6, p=0.47). Children with mild bronchiectasis had a weak insignificant relationship with either MPA size (r=0.04, p=0.57) or MPA-to-AA ratio (r=0.04, p=0.35). In children without bronchiectasis, MPA size was positively associated (r=0.91, p=0.01) but the MPA-to-AA ratio was negatively associated (r=-0.28, p=0.16) with age at scan.

Table-1: Demographic, radiological and clinical parameters

	All (n=26)	Male (n=7)	Female (n=19)
Age in years (Median)	10.9 (SD±3.6)	10.5 (SD±4.5)	11 (SD±3.3)
Age in years at time of scan (Mean)	8 (SD±3.9)	8.5 (SD±4.3)	7.6 (SD±3.8)
Height cm (Mean)	132	136	128
Situs Inversus	7	4	3
MPA size in mm(mean)	17.15 (SD±3.5)	18 (SD±3.6)	16.2 (SD±3.3)
MPA-to-AA ratio (Mean)	0.97 (SD±0.1)	1.0 (SD±0.11)	0.97 (SD±0.1)
Bronchiectasis(n)	19	4	15

Table-2: Relationship of age-adjusted measurements of MPA diameter and MPA-to-AA ratio with bronchiectasis

	No bronchiectasis (n=10)	Mild bronchiectasis (n=16)	Severe bronchiectasis (n=12)
MPA-to-AA ratio (Mean)	0.92	0.98	1.00
Pearson coefficient for MPA size	0.91 (0.01)	0.04 (p=0.57)	0.59 (p=0.06)
Pearson coefficient for MPA/Asc Ao	-0.28 (p=0.16)	0.04 (p=0.35)	0.6 (p=0.47)

Table-3: MPA size and MPA: Ascending Aorta in individual patients with bronchiectasis

	Age at scan(years)	MPA size(mm)	MPA-to-AA ratio	Bronchiectasis
1st patient	10	20	1.00	Mild
	11	20.6	0.96	Mild
	14	24.1	1.18	Severe
2nd patient	7	13.9	0.78	Mild
	9	16.6	0.89	Severe
3rd patient	2	13.2	0.98	None
	3	13.4	0.98	None
	5	16.9	1.07	Mild

Figure 1 shows the spread of the MPA-to-AA ratio in the whole group and is expressed as percentages. This is consistent with earlier studies. Serial measurements of 3 patients with a minimum of two HRCT showed that MPA size increased markedly when bronchiectasis progressed from mild to severe (Table 3). We also studied variations in measurements of ascending and descending aorta in children with bronchiectasis (Figure-2). Both can be interchangeably used if the image quality is not good for one of them (r=0.6).

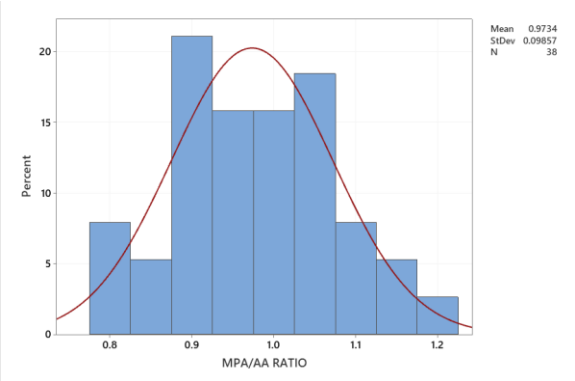


Figure-1: Distribution of MPA-to-AA ratio as percentages

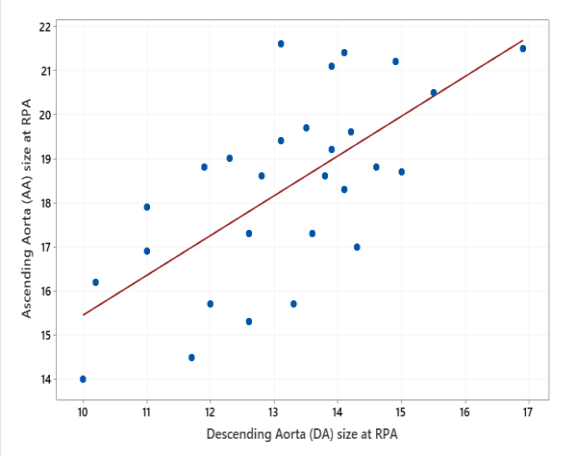


Figure-2: Ascending and descending aorta measurements in children with bronchiectasis

DISCUSSION

Regular assessment of lung function is central to the management of PCD. The choice of a specific lung function test depends mostly on the age of the child and the availability of tests. PCD has been associated with a gradual decline in lung function from an early age. Disease progression is monitored by doing tests like spirometry impulse oscillometry, (IOS), nasal nitric oxide, multiple breath washes out and chest imaging.[16] Maglione *et al* reviewed the relationship of spirometry indices with CT chest findings and stated that in non-CF bronchiectasis, HRCT lung changes may occur despite normal spirometry.[9] HRCT chest is considered a reliable method for defining structural changes in the airway and parenchyma.[17] Many studies have mentioned radiological characteristics of bronchiectasis in PCD.[18] There is not enough epidemiological data to assess the global burden of bronchiectasis in childhood, although extrapolation of published data suggests that prevalence ranges from 0.2–735 cases per 100 000 children.[19]In children, bronchiectasis is characterised by persistent (>3) episodes of chronic productive cough of greater than 4 weeks duration, associated with the chest computed tomography (CT) finding of a ratio between the inner airway and the outer vessel diameter ≥0.80.[20]

At our centre, spirometry or IOS is done on each hospital visit whereas HRCT is done once every three or four years. This approach is based on the local guideline considering the frequency of visits to our specialised tertiary care centre and compliance with treatment protocols. Deciding on the frequency of doing CT chest and preventing repeated exposure to ionising radiation is a clinical decision that needs careful attention. We hypothesized that MPA diameter and MPA-to-AA ratio can be used in conjunction with bronchiectasis to describe the severity of the disease. Greenberg *et al* published normative data for main and branch pulmonary artery measurements using 1-mm collimation double-oblique reconstructions for children between 0 and 18 years of age.[21] They excluded any patient with congenital heart disease or significant pulmonary disease. MPA was measured between the pulmonary valve and the bifurcation point. There were considerable gender differences for RPA size but not for MPA and LPA size. The authors put this down to a small study sample. One previous study correlated MPA and branch pulmonary artery diameter with a child's age. All measurements in this study were performed on axial reconstruction.[22] The CT scoring system in PCD is based on comparing structural changes associated with the disease.[23] Many scoring systems are validated in adults which can be modified for children. Modified Reiff, Bhalla, modified Brody and Heilbeich are the commonly used scoring systems in PCD.[24,25]

We divided the study group into children with or without bronchiectasis. In our study, there was significant concordance of the MPA-to-AA ratio with the severity of bronchiectasis. Unlike mild or no bronchiectasis, severe bronchiectasis was linked to a higher MPA-to-AA ratio (Table 2). This ratio was ≥1 in most of the patients (Figure1). Furthermore, a lack of positive association of the MPA-to-AA ratio with mild bronchiectasis might be indicative of potentially reversible parenchymal changes. It may also indicate

a negligible effect of mild bronchiectasis on vascular size, i.e., MPA, AA or DA size. MPA size(diameter) was positively related to all grades of bronchiectasis; the most significant association was present when there was no bronchiectasis. On its own, MPA (diameter) cannot differentiate children with or without bronchiectasis. An interesting finding from our study was a disproportionate increase in the size of MPA when patients developed bronchiectasis or when it progressed from mild to severe (Table-3). We did not use z scores as the data for controls in the study by Greenberg et al was insufficient to match age groups in our study. In children with bronchiectasis, the size of the descending aorta increases in parallel to the ascending aorta and can be used as an alternative to ascending aorta if the image quality does not allow ascending aorta to be measured correctly (Figure-2).

Like our cohort, Compton et al found a positive correlation between age-dependent MPA size and bronchiectasis in a relatively big group of 400 patients on HRCT chest series.[26] The authors were of the view that a slightly larger MPA segment in comparison to ascending aorta on HRCT does not support a diagnosis of pulmonary hypertension. Recently MRI has been used increasingly to detect bronchiectasis in adults but it is yet to become a preferred choice in paediatrics.[27] Its use in children has certain limitations like reduced access to technology and long acquisition times. Eichinger *et al* introduced an MRI scoring system for assessing CF lung disease in adults which can be adapted for the paediatric population.[28]

Our main limitation was a small sample size but considering this is a pilot study, all patients at our centre were included. The second limitation was not including age-matched controls. We could not get approval from the IRB committee to facilitate this. A future study with matched controls is needed to consolidate conclusions from our study. Finally, none of our patients had pulmonary hypertension on transthoracic ECHO and therefore we could not test our hypothesis that MPA or MPA-to-AA ratio can be used as surrogate markers for pulmonary hypertension in PCD. A larger study is needed to assess this.

CONCLUSIONS

This is the first study looking at MPA size and MPA: Ascending aorta in children with PCD. MPA size cannot differentiate children with or without bronchiectasis however MPA-to-AA ratio correlates well with severe bronchiectasis compared to mild bronchiectasis.

AUTHOR CONTRIBUTION

AZ was responsible for conceptualization, design, and literature search. AZ and MSQ contributed to the analysis and manuscript writing. MSQ analysed all the images and submitted all measurements. SA aided with the data collection, analysis and manuscript writing.

Declaration of conflicts of interest

The author declares no conflict of interest.

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Address for Correspondence:

Saba Ayub, Address: House No. 66, Lane 4, Sector C, Askari 14, Islamabad-Pakistan
Cell: +92 321 516 1481
Email: sabaayub.172@gmail.com