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A non-invasive method of predicting pulmonary hypertension using plain CT chest in correlation with 2d echocardiography

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Abstract
The aim of the study is to evaluate and compare the Plain CT based different vascular measurements in patient with probable pulmonary hypertension and in normal subjects. Images acquired using routine NCCT protocol on 16 slice Toshiba Alexion CT machine and. Reconstructed images were studied in full magnification on standardized media stinal window settings of (W:400/L:20). The widest diameters perpendicular to the axis of main pulmonary artery, right pulmonary artery, left pulmonary artery, ascending aorta and descending aorta are measured using calipers. These respective measurements of 50 normal subjects were compared to the 20 probable pulmonary hypertensive group diagnosed using standard2D Echocardiography criteria.

The measurements of MPA,RPA,LPA,MPA/AAo and MPA/DAo in normal subjects are 2.33(SD-0.31),1.84(SD-026),1.74(SD-0.25),0.82(SD-0.10) and 1.06(SD-0.22).The respective measurements in probable pulmonary hypertension group are 3.58(SD-0.30),2.57(SD-0.41),2.71(SD-0.49),1.11(SD-0.16) and 1.47(SD-0.30), which are comparatively higher and statistically significant (P value <0.01).

In our study, except the MPA/Dao, rest all measurements show positive correlation. The data was statistically analyzed using Graph pad Prism 8.4.2 and different tools used are two tailed t test, histogram analysis, Pearson correlation and sensitivities & specificities using receiver operating curves (ROC). The upper limits proposed in our study in predicting pulmonary hypertension are MPA 2.85 (sensitivity -95% and specificity – 96%),RPA2.22 (sensitivity – 80% and specificity – 92%), LPA 2.22 (sensitivity – 85% and specificity – 96%), MPA/AAo 1.04 (sensitivity – 80% and specificity – 92%) and MPA/DAo (sensitivity – 90% and specificity – 90%).

The various Plain CT based vascular measurements have got higher cut offs and are statistically significant in probable pulmonary hypertensive group when compared to normal subjects. Hence, Plain CT chest along with 2D Echocardiography can be used as a preliminary noninvasive evaluation of pulmonary hypertension before going for invasive right heart catheterization and thus delay in management can be prevented.

Keywords: PH: Pulmonary hypertension, MPA: Main pulmonary artery, MPD: Main pulmonary artery diameter, RPA.

Introduction

Pulmonary hypertension is a representative hemodynamic condition characterized by high arterial pressures of more than 25mm Hg, measured at catheterization of right heart, regardless of underlying disease [1]. Dana point classification system is an etiology-based categorization of pulmonary hypertension into groups and subgroups and is widely used by clinicians in regular practice [2]. PH being a progressive disease-causing chronic elevation of pulmonary arterial pressures and resistance, marked by continuous vascular proliferation and remodeling [3] leading to right ventricle dilatation and hypertrophy. It usually marks poor prognosis [3, 4, 5, 6]. Right heart catheterization is the only invasive method available to measure pulmonary pressures, resistance, and cardiac output in one go, hence considered as gold standard method in establishing diagnosis of PH. The systemic evaluation of PH patients include detailed clinical examination and various investigations like Electrocardiography, Blood tests and immunology, pulmonary function tests, Arterial blood gas analysis, Cardiopulmonary exercise testing and Imaging techniques like Ventilation perfusion scans, Echocardiography, CT pulmonary angiography, Cardiac CT and Cardiac MRI [7].

The nonspecific and overlapping clinical features with other pulmonary and cardiac conditions makes it a clinical challenge [8, 9, 10] and so various imaging investigations are sort for. Thus, radiologists are often the first persons to raise a strong suspicion for PH along with the giving clues to the underlying conditions responsible for PH. Our study is mainly focused at studying the various CT based vascular measurements that would suggest the diagnosis of PH before the definitive invasive technique of right heart catheterization.

Materials and Methods

The present prospective study is conducted during 2019-2020, for a period of 6 months in a rural tertiary care hospital in Nalgonda after acquiring proper patient consent and hospital ethical committee clearance. The aim of the study is to evaluate and compare the plain computed tomography based pulmonary artery measurements in patients with probable pulmonary hypertensive diagnosed on 2D Echocardiogram with normal subjects. The objectives are to determine the variations in main pulmonary artery diameters, branched – right and left pulmonary artery diameters and the ratio of the diameters of main pulmonary artery and ascending aorta and descending aorta between the two study groups. The normal study group consists of 50 subjects, selected based on the criteria of lack of known cardiac, thoracic disease associated with elevation of pulmonary flow/pressure, mediastinal disease, and chest/mediastinal radiotherapy, which can influence the measured variables.

The 20 subjects in probable pulmonary hypertensive group are selected based on the 2D echocardiography using the combination of tricuspid regurgitant velocity, right ventricular size, interventricular septal function, inferior vena cava diameter fluctuations with respiratory cycle, systolic right atrial area, pattern of systolic flow velocity and early diastolic pulmonary regurgitant velocity, and diameter of the pulmonary artery [11] (Table – 1 and 2)

Routine Plain CT chest was performed in both group of patients usingroutine NCCT chest protocol on 16 slice Alexion Toshiba CT machine with patient in supine position in suspended deep inspiration with arms extended overhead. The acquired images were reconstructed to 1.2-1.5mm thickness and reviewed on workstation at standardized mediastinal window settings of (W:400/L:20). The region of ascending aorta, descending aorta and pulmonary artery bifurcation was magnified to full screen size. The widest diameter perpendicular to long axis of MPA is measured with computer calipers at the level of pulmonary artery bifurcation. Similarly, the widest diameters perpendicular to long axis of RPA, LPA, Ascending aorta, and Descending aorta are also measured in the near sections of bifurcation of pulmonary artery (Figures 1 to 4)

Table 1: Echocardiographic findings suggesting the diagnosis of probable pulmonary hypertension (PH)

Peak tricuspid regurgitation velocity(m/s)	Presence of other echocardiographic "PHsigns"	Echocardiographic probability of PH
< 2.8 or not measurable	No	Low
< 2.8 or not measurable	Yes	Intermediate
2.9 – 3.4	No	
2.9 – 3.4	Yes	High
>3.4	Not required	

Courtesy: Guidelines and recommendations- Echocardiographic assessment of pulmonary hypertension: a guideline protocol from the British society of echocardiography, 2018.

Table 2: Echocardiographic signs suggesting pulmonary hypertension used to assess the probability of PH in addition to tricuspid regurgitation velocity (m/s)

A: The ventricles	B: Pulmonary artery	C: Inferior vena cava and right atrium
Right ventricle / Left ventricle basal diameter ration >1.0	Right ventricular outflow doppler acceleration time <105ms and/or mid systolic notching	Inferior cava diameter >21mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2m/s	Right atrial area (end systole) >18cm^2.
	Pulmonary artery diameter >25mm	
Echocardiographic signs from at least two different categories(A/B/C) from the list should be present to alter the level of echocardiographic probability of PH.		

Courtesy: Guidelines and recommendations- Echocardiographic assessment of pulmonary hypertension: a guideline protocol from the British society of echocardiography 2018.

Results

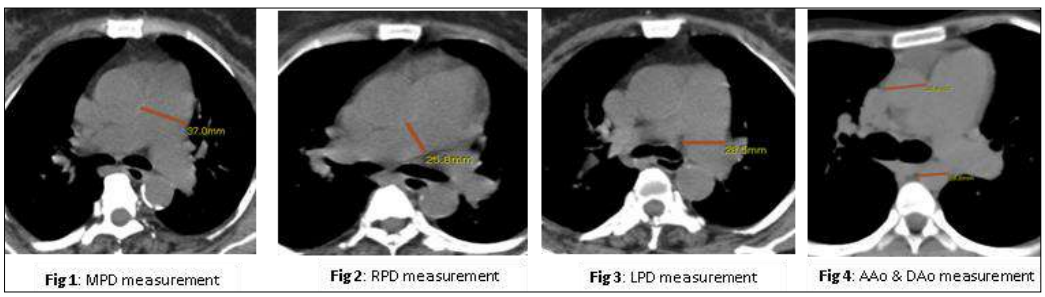


Fig 1, 4: Are the representative images demonstrating the points at which appropriate CT based measurements of Main pulmonary artery diameter (MPD), Right pulmonary artery diameter (RPD), Left pulmonary artery diameter (LPD), Ascending aorta and Descending aorta measurements are taken for the two study groups – Normal and Probable PAH.

Table 3: Age distribution in two study groups

Age (inYrs)	Normal subjects(n=50)	Probable PH group (n=20)
10-19	3	2
20-29	6	1
30-39	9	2
40-49	10	3
50-59	2	1
60-69	16	11
70-79	4	0
Total	50	20

Table 4: Gender distribution in two study groups

Gender distribution	Normal subjects(n=50)	Probable PH group (n=20)
Males	35	15
Females	15	5
Total	50	20

Table 5: Frequency distribution of MPD measurements

MPD (in cms)	Normal subjects(n=50)	Probable PH group (n=20)
1-1.49	0	0
1.5-1.99	8	0
2-2.49	23	0
2.5-2.99	17	2
3-3.49	2	2
3.5-3.99	0	16
Total	50	20

Table 6: Frequency distribution of RPD measurements

RPD (in cms)	Normal subjects(n=50)	Probable PH group (n=20)
1-1.49	4	0
1.5-1.99	38	2
2-2.49	6	4
2.5-2.99	2	12
3-3.49	0	2
3.5-3.99	0	0
Total	50	20

Table 7: Frequency distribution of RPD measurements

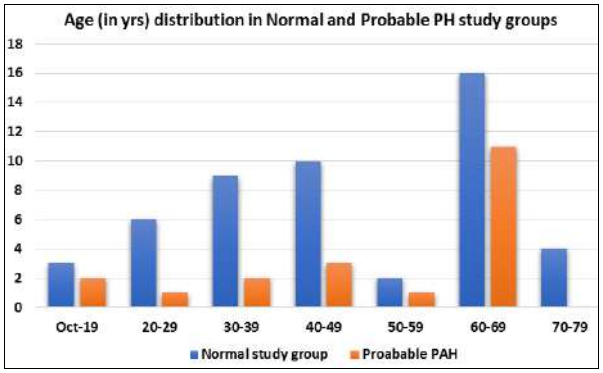
LPD (in cms)	Normal subjects(n=50)	Probable PH group (n=20)
1-1.49	4	0
1.5-1.99	38	0
2-2.49	6	6
2.5-2.99	2	11
3-3.49	0	1
3.5-3.99	0	2
Total	50	20

Table 8: Frequency distribution of MPD/DAo measurements

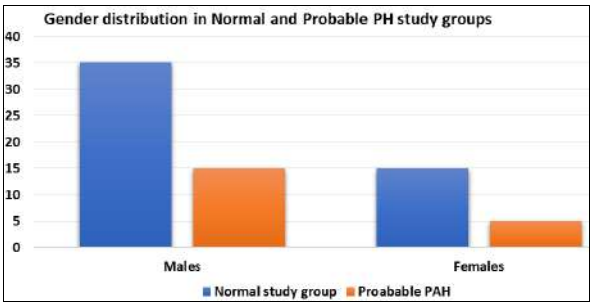
MPD/DAo	Normal subjects(n=50)	Probable PH group (n=20)
0.5-0.99	18	0
1.0-1.49	27	16
1.5-1.99	5	2
2.0-2.49	0	2
2.5-3	0	0
Total	50	20

Table 9: Frequency distribution of MPD/AAo measurements

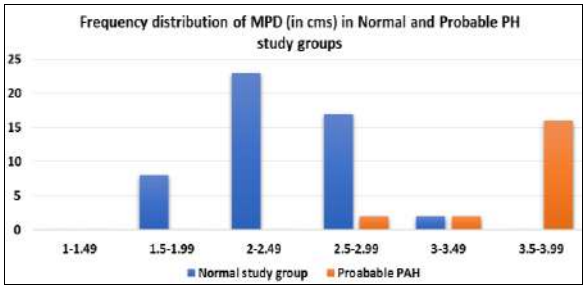
MPD/AAo	Normal subjects(n=50)	Probable PH group (n=20)
0.5-0.99	44	3
1.0-1.49	6	17
1.5-1.99	0	0
2.0-2.49	0	0
2.5-3	0	0
Total	50	20



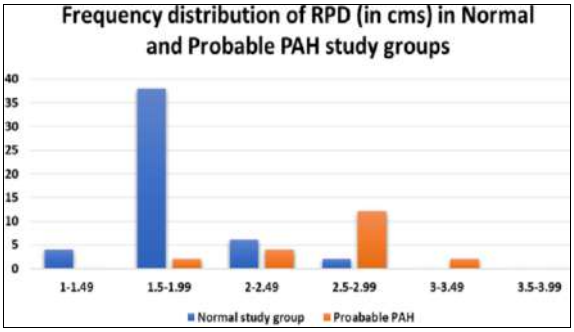
Graph 1: Age distribution in two study groups



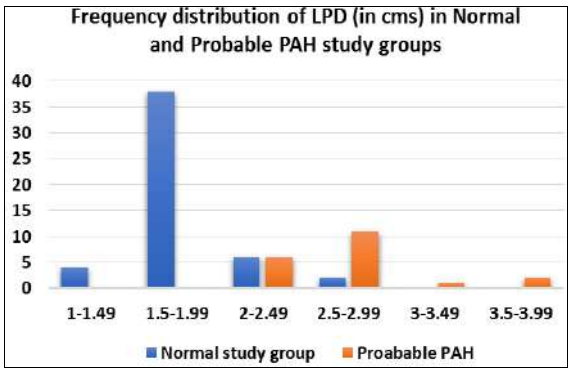
Graph 2: Gender distribution in two study groups



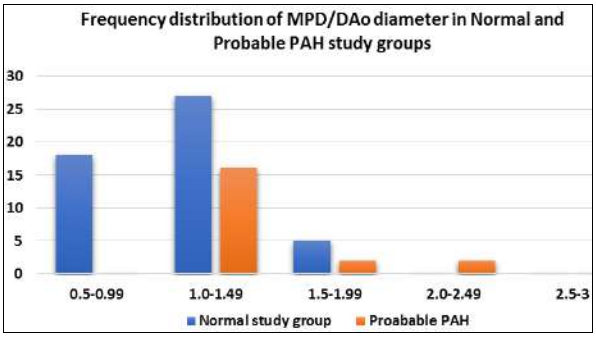
Graph 3: Frequency distribution of MPD measurements



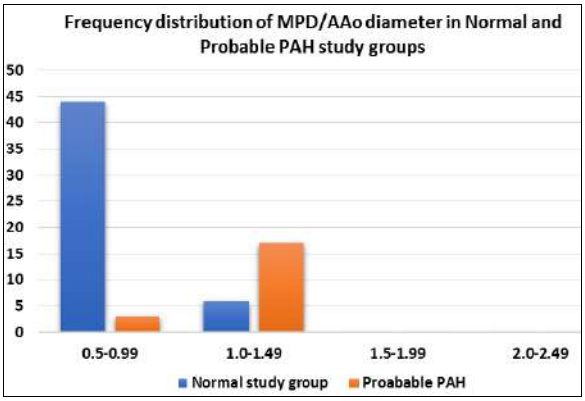
Graph 4: Frequency distribution of RPD measurements



Graph 5: Frequency distribution of LPD measurements



Graph 6: Frequency distribution of MPD/DAo measurements



Graph 7: Frequency distribution of MPD/AAo measurements

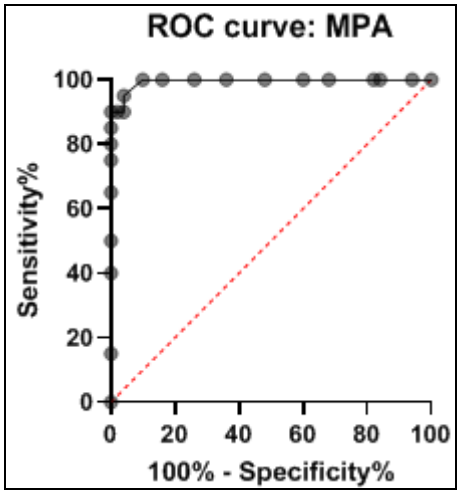


Fig 5: ROC curve - MPD

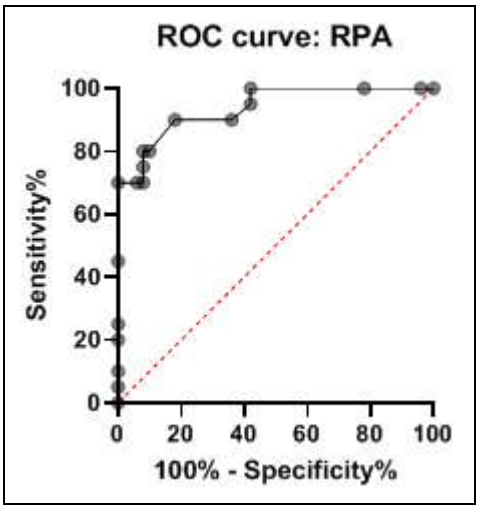


Fig 6: ROC curve – RPD

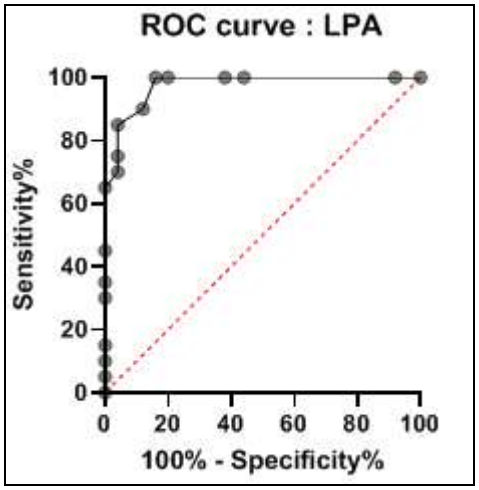


Fig 7: ROC curve - LPD

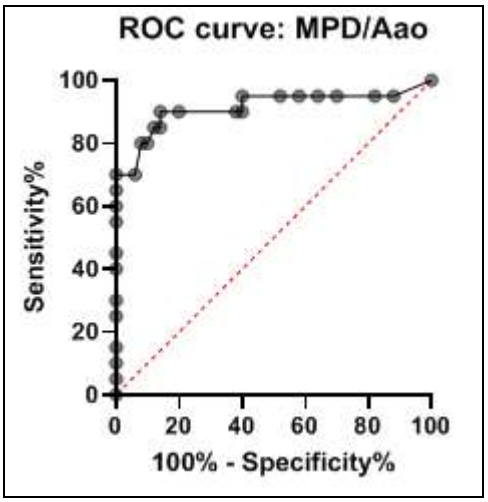


Fig 8: ROC curve – MPD/AAo

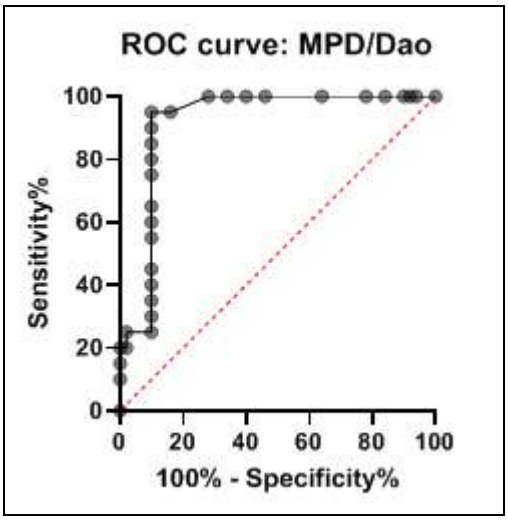


Fig 9: ROC curve – MPD / DAo

Fig 5, 9: Receiver operating curves of the measured variables - MPD, RPD, LPD, MPD/AAo and MPD/DAo to calculate the sensitivities and specificities at different points.

The same measurements are calculated separately for control group with normal subjects and test group, probable PH diagnosed on 2D ECHO and then cutoff values are compared between two groups using different statistical tools.

The statistical analysis of the acquired data was done using GraphPadPrism8.4.2. The significance of the mean values of the different variables between two groups are calculated individually using Two tailed t test, The frequency distribution of the data was calculated using histogram analysis, the correlation between different variables with in the probable PH groups are calculated using Pearson correlation-r and finally the receiver operative curves are used to calculate sensitivities and specificities at different points on the graph.

In our study, the predominant age group was in the range 60-70 years and predominant gender being male in both the study groups (Graph 1,2 and Table 3,4).

The frequency distribution of all the evaluated variables – MPD, RPD, LPD, MPD/AAo and MPD/DAo in both study groups are tabulated and represented as bar diagrams (Graph 3to7 and Table 5to9). The histogram analysis of the data (table10) shows the measurements of MPA,RPA,LPA,MPA/AAo and MPA/DAo in normal subjects are 2.33 (SD-0.31), 1.84(SD-026),1.74(SD-0.25),0.82(SD-0.10) and 1.06(SD-0.22) and the respective measurements in probable pulmonary hypertension group are 3.58(SD-0.30),2.57(SD-0.41),2.71(SD-0.49),1.11(SD-0.16) and 1.47(SD-0.30), which are comparatively higher and statistically significant (P value <0.01).

The upper limits proposed in our study in predicting pulmonary hypertension are MPA 2.85(sensitivity -95% and specificity – 96%),RPA2.22 (sensitivity – 80% and specificity – 92%), LPA 2.22(sensitivity – 85% and specificity – 96%), MPA/AAo 1.04 (sensitivity – 80% and specificity – 92%) and MPA/DAo (sensitivity – 90% and specificity – 90%) represented in table 11.

The Pearson correlation of different variables (figure 10) in probable PH study group shows strong correlation among MPA, RPA, LPA and MPA/AAo but poor correlation with MPA/DAo.

Table 10: Comparison of the Mean and SD values of the MPD, RPD, LPD,MPD/AAo and MPD/DAo in normal and probable PH study groups.

S. N.	Variables measured	Normal (in cms)	Probable PH(in cms)
1	Main pulmonary artery diameter	2.33+/-0.31	3.58+/-0.30
2	Right pulmonary artery diameter	1.84+/-0.26	2.57+/-0.41
3	Left pulmonary artery diameter	1.74+/-0.25	2.71+/-0.49
4	MPD/Asc aorta diameter	0.82+/-0.10	1.11+/-0.16
5	MPD/Desc aorta diameter	1.06+/-0.22	1.47+/-0.30

All the mean measurements of MPD, RPD, LPD, MPD/AAo and MPD/DAo are significantly greater in probable PAH group when compared to normal subjects (two tailed t test: *p<0.01*).

Table 11: The upper cut off values of the MPD, RPD, LPD, MPD/AAo and MPD/DAo inprobable PH study group along with the sensitivity and specificities calculated.

Variables measured	Upper limit Cut off	sensitivity	specificity
MPD	>2.85	95%	96%
	>3.2		100%
RPD	>2.22	80%	92%
	>2.55		100%
LPD	>2.25	85%	96%
	>2.55		100%
MPD/AAo	>1.04	80%	92%
	>1.09		100%
MPD/DAo	>1.22	90%	90%
	>1.78		100%

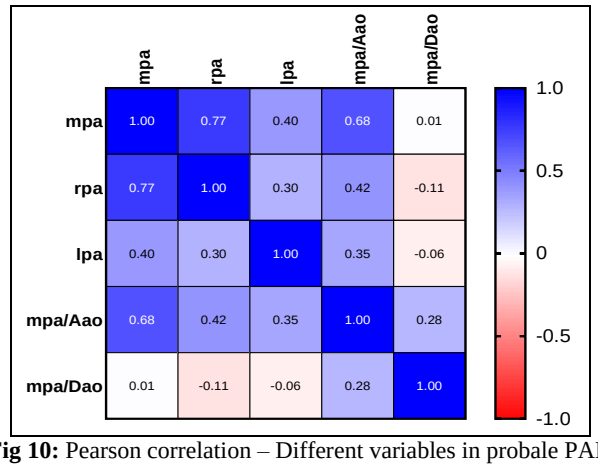


Fig 10: Pearson correlation – Different variables in probale PAH group Blue color – strong correlation (>1); Red color – strong non correlation (<1)

Discussion

The factors that influence the pulmonary vessels size are complex and depend on physiological and pathological factors. Pressure in one factor and others include blood flow, vessel compliance [12], peripheral resistance, pathology within the vessel, sex, and body constitution [9] and physical properties of lung [10].

As PH is defined in terms of increased pressure within the pulmonary vessels, which usually causes at least some distension of these involved vessel, this is used as animaging criterion in evaluation of Pulmonary Hypertension. Different variables are studied in detail and respective cut offs were given by different studies.

Our study is mainly aimed at comprehensive evaluation of all the possible variables on non-contrast CT study – Main pulmonary artery, Right pulmonary artery, Left pulmonary artery, Ratio of Main pulmonary artery to ascending aorta and Ratio of Main pulmonary artery to descending aorta.

Pulmonary artery dimension varies with cardiac cycle, respiratory movements, and technical parameters like CT window settings and contrast [13] and thus the ratio of MPD and Ascending aorta is used in different studies to overcome these difficulties. In our study, we have calculated the ratio with ascending as well as descending aorta in the same

section to analyze the respective variations.

The role of MPD and its statistical significance in prediction of pulmonary hypertension was not completely supported in various other studies [14, 15, 16, 17, 18]. However, there are studies supporting the same.

The kuriyama *et al.* [14] study in 1984 showed MPD as a valuable noninvasive method of predicting PH and gave the normal MPD diameter measured in 26 healthy study controls as 2.42+/-0.22cm and age matched MPD measurements in catheterize proven PH patients as above 2.86cm, with a sensitivity and specific of 69% and 100% respectively. Moore *et al.* [12] study in 1988 demonstrated the same with upper limit of MPD at 3.6+/-0.6cm.

In 1996, Schimdt *et al.* [19] study gave the upper limits of MPD at 2.8cm, RPD at 1.6cm and LPD at 1.6cm for the diagnosis of pulmonary hypertension and in 1997, the Haimovici *et al.* [20] study proposed the upper limits of MPD at 3.3 +/- 1.1cm and LPD at 2.5+/-0.8cm.

Near Corson *et al.* [21] conducted a similar study in 2014 in relatively large study group of 175 PH patients and gave upper cutoff value for MPD as 2.9cm with 89% and 83% sensitivity and specificity respectively and ratio of MPD and Aorta diameter > 1 with 89% and 82% sensitivity and specificity respectively.

Finally in our study, we have taken a comprehensive measurements of MPD,RPD,LPD,MPD/AAo and MPD/DAo in correlation with 2D Echocardiogram and proposed the upper cutoffs as 2.85cm for MPD with 95% sensitivity and 96% specificity, 2.22cm for RPD with 80% sensitivity and 92% specificity, 2.25cm for LPD with 85% sensitivity and 96% specificity, 1.04 for MPD/AAo with 80% sensitivity and 92% specificity and 1.22 for MPD/DAo with 90% sensitivity and 90% specificity.

Conclusion

The various Plain CT based vascular measurements have got higher cut offs and are statistically significant in probable pulmonary hypertensive group diagnosed on 2D echocardiogram when compared to normal subjects. Hence, Plain CT chest along with 2D Echocardiography can be used as a preliminary noninvasive evaluation of pulmonary hypertension before going for invasive right heart catheterization and thus delay in management can be prevented.

However, the upper limits proposed in the study may slightly vary with the already existing values in the literature. The reasons could be selection of subjects, racial group, small study group and importantly plain CT study.

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