CT FINDINGS OF PULMONARY HYPERTENSION

A thesis submitted to the University of Arizona College of Medicine – Phoenix
in partial fulfillment of the requirements for the Degree of Doctor of Medicine

Akash Patel

Class of: 2017

Mentor: Dr. Mary Connell, MD

Abstract

Primary pulmonary hypertension (PPH) has an extremely poor prognosis with a mean survival time of 2-3 years from time of diagnosis. Hemodynamically, PPH is defined with a mPAP of ≥ 25 mm Hg. Currently, RHC is the gold standard for measuring the arterial pressures and diagnosing PPH; however, it is an incredibly invasive procedure. Our study will show whether CT angiography can be considered as a non-invasive alternative for diagnosing PPH. Studies in the past have shown CT measurements of the MPAD and MPAD/AAD ratio having strong correlations with PPH. In addition to those measurements, we want to show if other CT parameters also have a correlation with PPH. Some of these novel measurements include the interventricular septal deviation and the Elizabeth Taylor sign. The interventricular septum is normally bowing to the right in a non-pathological state. If it is straight or bowing to the left, this will indicate increased right ventricular pressures which would be indicative of PPH. Straight will indicate increased RV pressures, and bowing to the left will be considered markedly increased RV pressures. The Elizabeth Taylor sign is the ratio of the diameter of the segmental bronchi and its corresponding artery. We will hypothesize that the artery will be much larger than the bronchi in patients with PPH. Other measurements will include the left and right pulmonary arteries. This study is a retrospective review of subjects who underwent an otherwise unremarkable CT pulmonary artery angiogram. Subjects with pulmonary embolism or other acute pulmonary diseases are excluded. For each subject, the following CT findings are obtained: main pulmonary artery diameter (mPAD), ratio of mPAD to ascending aorta, right and left pulmonary artery diameters, ratio of segmental pulmonary artery to corresponding bronchus, and interventricular septal displacement. Straightening of the interventricular septum qualifies as increased right ventricular septal pressure and right-to-left bowing of the septum qualifies as a marked increase. Mean pulmonary artery pressure measured on any prior/subsequent RHC or echocardiogram within 3 months of the CT is recorded. Any past medical history of connective tissue disease is noted. Descriptive data are calculated and correlations are done to assess for presence and strength of associations among variables. Data from 484 subjects are collected. Incidence rate of pulmonary hypertension isv13% (n=63). 52%

(n=33) of the subjects with pulmonary hypertension are female with an average age of 55 years. mPA diameter ($p<0.001$), mPA:AA ratio ($p<0.001$), right ($p<0.001$) and left pulmonary artery ($p=0.004$) diameters are predictors of pulmonary hypertension. sPA:B ratio ($p=0.08$) and interventricular septal displacement ($p=0.96$) are not predictive of pulmonary hypertension. This study supports an association of mPA diameter, mPA:AA ratio, right and left pulmonary artery diameters with pulmonary hypertension diagnosed by RHC or echocardiogram. Prospective research is warranted to confirm and establish threshold values for each variable. Currently, an invasive RHC remains the most accurate method of diagnosis. Correlating CT findings with pulmonary hypertension would allow clinicians to use CT as a noninvasive screening tool.

Research Question

1. Which CT findings/measurements correlate with pulmonary hypertension?

   CT findings/measurements:

   Main pulmonary artery diameter, ratio of main pulmonary artery: ascending aorta diameter, right pulmonary artery diameter, left pulmonary artery diameter, increased right ventricular septal pressure, ratio of segmental pulmonary arteries: corresponding segmental bronchi in the right lower lobe and left lower lobe

Hypothesis

There will be a correlation between the CT findings and primary pulmonary hypertension.

Objectives

1. ***Primary objectives:***

   To correlate CT findings/measurements with pulmonary hypertension diagnosed by echocardiogram and right heart catheterization.

2. ***Secondary objectives:***

   To determine the incidence rate of primary pulmonary hypertension in our population.

Table of Contents

Figures and Tables

Introduction, Significance, Rationale

Primary pulmonary hypertension (PPH) is a severe disease that often implicates markedly decreased activity tolerance and eventually right sided heart failure. It has an incredibly poor prognosis; mean survival from time of diagnosis is only 2-3 years (4). PPH is defined hemodynamically by a mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg accompanied by pathological changes in the pulmonary precapillary vessels (3). The disease also has nonspecific presenting symptoms, similar to those of pulmonary embolism and multiple other cardiac/ pulmonary etiologies: shortness of breath, dyspnea on exertion, and/or chest pain.

Patients with PPH do have improved survival time with the new therapeutic strategies today (3). However, these therapeutic strategies are limited by their delayed implementation due to the late diagnosis of the disease. Explanations for delayed discovery of PPH in patients could be explained by the non-specific signs and symptoms of the disease itself and the limits of the diagnostic tools implemented. Echocardiography is often used as a screening tool but is not considered the gold standard in the measurement of pulmonary arterial pressure. Currently, right heart catheterization (RHC) remains the most accurate method of diagnosis (1). However, RHC is an invasive procedure with significant risks, requiring intensive monitoring and therefore limiting its use. Patient evaluation using CT has been used to diagnose pulmonary embolism and other acute pulmonary diseases. Patients with chronically elevated pulmonary arterial pressures have a resulting dilation in the pulmonary arteries and right ventricle which suggests the efficacy of CT findings in diagnosing PPH (5-9). Furthermore, recent studies have begun to evaluate noninvasive imaging modalities and suggest that certain measurements on CT examination correlate with pulmonary hypertension (1). These measurements include the mPAD and mPAD/Ascending aorta diameter ratio (1,3).

In addition to CT measurements already shown to have associations with PPH, we will be examining findings not yet fully described in the setting of PPH. We plan to correlate our CT findings/measurements (including a novel measurement of increased right ventricular septal pressure) with pulmonary hypertension diagnosed by right heart catheterization and

1

echocardiogram. Our initial plan is to retrospectively review patients who recently presented to the emergency department (since January 1, 2013) and underwent an otherwise unremarkable CT pulmonary artery angiogram. We will correlate our findings/measurements from the CT to the mPAP measured on any prior/subsequent right heart catheterization or echocardiogram within 6 months of the CT. Our ultimate plan is to develop a protocol based on our findings to prospectively recommend appropriate patient management.

Although this initial study will be a retrospective review, we realize that we may encounter patients with CT findings of primary pulmonary hypertension who went undiagnosed. Given the poor prognosis of primary pulmonary hypertension, we will make a reasonable effort to contact the patients via phone and mail, and recommend them to seek further evaluation to confirm the diagnosis.

Materials and Methods

We will be making the following CT measurements: mPAD, mPAD:AAD ratio, right pulmonary artery diameter, left pulmonary artery diameter, increased right ventricular septal pressure, ratio of segmental pulmonary arteries: corresponding segmental bronchi in the right lower lobe and left lower lobe. The CT measurements will be correlated with the mPAP measured on a prior/subsequent RHC or echocardiogram within 3 months of the CT pulmonary angiogram. Note: an mPAP ≥25mm Hg is defined as pulmonary hypertension.

Patient Selection

All patients presenting to the emergency department who underwent a CT pulmonary artery angiogram from October 1, 2013 to January 1, 2014 will be retrospectively examined for this study. Exclusion criteria will include causes of secondary PH such as a pulmonary embolism and other acute pulmonary diseases. Patient medical record numbers, date of births, gender, date of the CT, presence of connective tissue disease, and time difference between the RHC/echocardiogram and CT will be noted.

CT Technique

CT angiograms were taken of patients lying in the supine position during full inspiration. The CTs were performed using different scanners**.** The scans were read and analyzed using normal mediastinal windows. Helical CT scans were obtained with a 16-slice detector unit. 80-100 ml of non-ionic contrast were injected via 3ml/sec intravenously as part of the pulmonary angiogram protocol.

Interpretation

The CT scans will be examined by a radiologist and medical student as a blind study in which they will be unaware of the patient's diagnosis and RHC/echocardiogram readings.

Assessment

We will estimate the position of the interventricular septum on CT angiography axial images and grade it as normal (deviated to the right ventricle), straight, or bowing (deviated to the left ventricle). This will be indicative of the right ventricular pressures. Additionally, measurements of ≥29 mm for the mPAD will be considered as having a correlation with PPH.

Statistical Analysis

Patient characteristics and hemodynamic and CT measurements are expressed as mean ± SD. The statistically significant differences between the control and PH patient groups were analyzed with an independent sample test statistic (t test) for the normally distributed parameters and with the Mann-Whitney U test for those that were not. The tests were 2-tailed (P-value >|t|), and statistical significance was considered when $P < 0.05$. The receiver operating characteristic curve was used to assess the ability of the mPAD or mPAD/AAD ratio to predict PH by calculating both the sensitivity and specificity at different cutoff points. The interobserver and intraobserver variability for CT measurements was generated using Bland-Altman analysis. The statistically significant difference in mPAD measurements between PH groups was evaluated using the factorial analysis of variance test.

Results

Data from 484 subjects are collected. Incidence rate of pulmonary hypertension is 13% (n=63). 52% (n=33) of the subjects with pulmonary hypertension are female with an average age of 55 years.

mPA diameter ($p<0.001$), mPA:AA ratio ($p<0.001$), right ($p<0.001$) and left pulmonary artery ($p=0.004$) diameters are predictors of pulmonary hypertension. sPA:B ratio ($p=0.08$) and interventricular septal displacement ($p=0.96$) are not predictive of pulmonary hypertension.

Group Statistics

	High PASP>=30	N	Mean	Std. Deviation	Std. Error Mean
Age	0	79	52.70	15.574	1.752
	1	63	55.08	11.959	1.507
Main PA	0	79	27.8861	4.56572	.51368
	1	63	30.7302	6.26358	.78914
PAD/AAD	0	79	.9238752223	.1570827578	.0176731910
	1	63	.9743166541	.1880590225	.0236932098
RPA	0	79	20.5696	2.92506	.32910
	1	63	23.4603	3.71928	.46859
LPA	0	79	20.6329	2.88309	.32437
	1	63	22.7778	3.42874	.43198
RLL A:B	0	79	1.515893811	.4289011675	.0482551514
	1	63	1.742326038	.6840145784	.0861777365
LLL A:B	0	79	1.4753	.56742	.06384
	1	63	1.6710	.65126	.08205

Table 1: indicates the average values based on individual parameters with relation to pulmonary hypertension.
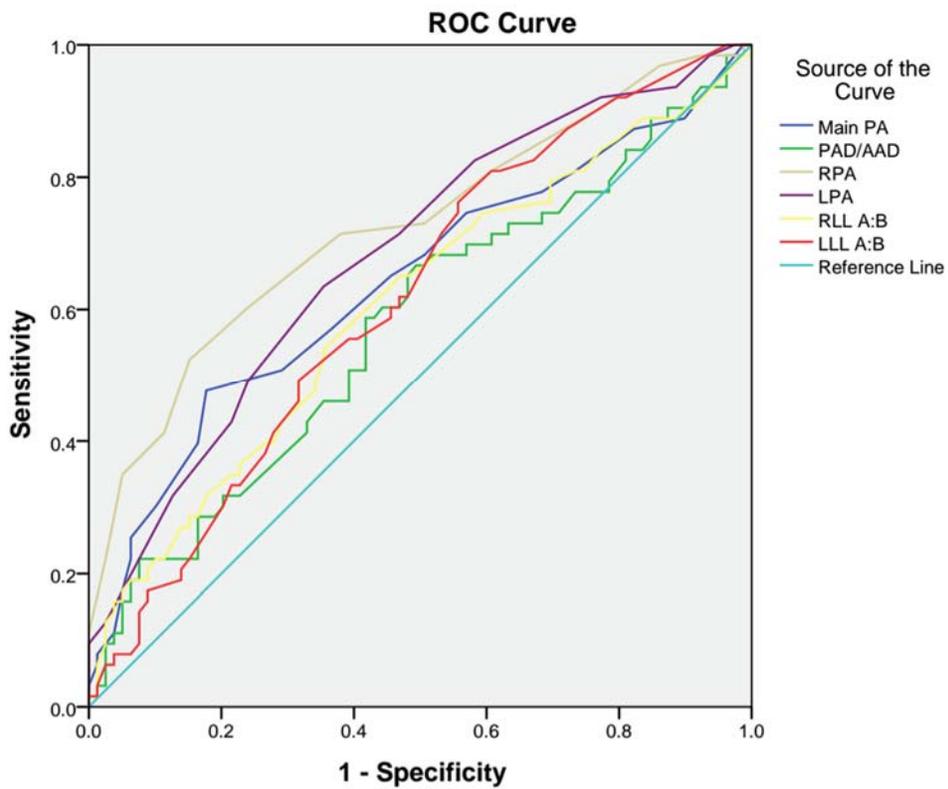
ROC Curve

Figure 1: Indicates the ROC curve for individual parameters. PAD/AAD has the highest sensitivity whereas the main PA has the highest specificity.

Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Main PA	.665	.067	.016	.534	.797
PAD/AAD	.580	.068	.248	.446	.713
RPA	.720	.061	.001	.601	.839
LPA	.662	.064	.018	.537	.788
RLL A:B	.645	.067	.035	.514	.775
LLL A:B	.632	.065	.055	.505	.760

The test result variable(s): Main PA, PAD/AAD, RPA, LPA, RLL A:B, LLL A:B has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Table 2: Indicates the average area under the curve with RPA having the highest confidence interval.

Discussion

This study supports an association of mPA diameter, mPA:AA ratio, right and left pulmonary artery diameters with pulmonary hypertension diagnosed by RHC or echocardiogram. Correlating CT findings with pulmonary hypertension allows clinicians to use CT as a noninvasive screening tool. Prospective research is warranted to confirm and establish threshold values for each variable.

Our study agrees with prior reports indicating that the size of the pulmonary arteries measured on CT does correlate with the incidence and severity of pulmonary hypertension. However, more specifically, our data indicated that the mPAD/AAD ratio had a higher correlation with pulmonary hypertension when compared to mPAD. The right pulmonary artery diameter and left pulmonary artery diameter showed significantly less correlation with the incidence of pulmonary hypertension; however, the left PAD indicated a better correlation than the left PAD. The other parameters we analyzed did not show significant correlation with pulmonary hypertension to suggest future use in a prediction model.

This research study is novel in analyzing the straightening of the interventricular septum relating to pulmonary hypertension. However, we were not able to detect straightening of the interventricular septum with enough incidence to have power. When straightening was detected, the patient did have pulmonary hypertension. Based on our limited data, this finding is not sensitive enough to be used as an evaluation of pulmonary hypertension though future studies are warranted.

Furthermore, we found that an mPAD/AAD ratio >1 and mPAD > or = 30 mm yielded the highest diagnostic accuracy. The combination of these two findings were able to detect pulmonary hypertension with relative accuracy. Using a higher threshold (>30 mm mPAD) lowered the sensitivity significantly but illustrated a greater specificity (~90%).

We think that using CT with an IV contrast bolus may potentially increase the appearance of false positives as it can give the appearance of a larger mPAD. Future studies are warranted to

minimize this bias in measurements. However, we are able to normalize much of this through the mPAD/AAD ratio. Selection bias was minimized as any patient with evidence of lung pathology was excluded from our study.

In conclusion, the mPAD and mPAD/AAD ratio are useful clinical tools for predicting pulmonary hypertension. Based on our current data, we think using mPAD of > or = 30 mm and mPAD/AAD ratio >1 appear to be the most accurate/useful parameters for predicting pulmonary hypertension. Future studies are warranted to make further conclusions regarding the straightening of the interventricular septum.

References

1. Mahammedi A, et al. Pulmonary Artery Measurements in Pulmonary Hypertension. J Thorac Imaging 2013; 28(2): 96-103.

2. Devaraj A, et al. Detection of Pulmonary Hypertension with Multidetector CT and Echocardiography Alone and in Combination. Radiology 2010; 254: 609-616.

3. Grubstein A, et al. Computed Tomography Angiography in Pulmonary Hypertension. IMAJ 2008; 10: 117-120.

4. Mclaughlin, Vallerie. "Comparison of survival in patients with pulmonary hypertension associated with fenfluramine to patients with primary pulmonary hypertension." *The American Journal of Cardiology.* 1366-1368. Print.

5. Moraes D, Localzo J. Pulmonary hypertension: newer concepts in diagnosis and management. *Clin Cardiol* 1997;10-676-82

6. Runo J. Loyd J. primary pulmonary hypertension. *Lancet* 2003;361:1533-44.

7. Budev MM, Arroliga AC, Jenning CA. Diagnosis and evaluation of pulmonary hypertension. *Cleve Clin* J Mol 2003; 70(Suppl 1):S9-17.

8. Bugnone A, Viamonte M, Garcia J. Imaging findings in HIB-related pulmonary hypertension: report of five cases and review of the literature. *Radiology* 2002;223:820-7

9. Hey JC, Scharf SM. Pulmonary arterial hypertension – the primary pulmonary hypertension syndromes. IMAJ 2003;5:298-303.