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Relationship of Main Pulmonary Artery Diameter to Pulmonary Arterial Pressure in Scleroderma Patients with and without Mild to Moderate Interstitial Fibrosis

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by

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ABSTRACT

Purpose: To determine the validity of main pulmonary artery diameter (MPAD) as a marker of pulmonary hypertension in scleroderma patients with and without interstitial lung disease (ILD).

Materials and Methods: We cross-referenced the radiologic database with medical records to identify patients with both computed tomography (CT) scans of the chest and right-heart catheterization separated by no more than six months. Computed tomography scans were reviewed to determine MPAD and extent of ILD for each patient. Ground glass opacity and fibrosis were individually scored by a single thoracic radiologist on a five-point scale. The same radiologist also determined the quality of delineation for the great vessels. MPAD was calculated based on the average of measurements taken from two separate observers. Mean pulmonary arterial pressures (mPAP) were determined by RHC. Patients were divided into either group A (n = 20) or group B (n = 27) based on the absence or presence of interstitial fibrosis respectively. Patients with available data from pulmonary function tests (PFTs) were divided into those with FVC > 70% predicted (Group C) and those with FVC $\leq$ 70% predicted (Group D). Groups were compared using either the Student t test or Mann-Whitney U test depending on the distribution of each variable under consideration. Either the Pearson correlation coefficient or the Spearman rank-correlation coefficient was calculated for each group to evaluate the relationship between MPAD and mPAP.

Results: Groups A and B were similar with regard to MPAD ($p = 0.28$) and mPAP ($p = 0.34$) upon Mann-Whitney U testing. MPAD was strongly correlated with mPAP in both Group A ($r = 0.68$, $p = 0.001$) and Group B ($r = 0.70$, $p < 0.0001$). The correlation between MPAD and mPAP in Group C ($r = 0.69$, $p = 0.002$) was substantially higher than that in Group D ($r = 0.42$, $p = 0.11$).

Conclusion: In our patient sample with scleroderma, MPAD is strongly correlated with mPAP and may indicate the development of pulmonary hypertension regardless of the presence of mild to moderate interstitial fibrosis. An increase in the severity of restrictive lung disease as measured by FVC appears to attenuate the correlation between MPAD and mPAP.

CHAPTER 1

INTRODUCTION

Scleroderma refers to a fibrotic thickening of the skin that frequently becomes clinically apparent in several different pathologic states involving connective tissue derangements of production and organization. Though strictly only a symptom, the use of this term has, over time, become synonymous with the disease known as systemic sclerosis (SSc). Regardless of how one chooses to use the label "scleroderma", the fibrotic mechanism underlying this finding may lead to other systemic manifestations that overlap across the various connective tissue diseases. As a model illness for which scleroderma is the most clinically evident symptom, SSc can involve many organs throughout the body and show marked heterogeneity in the time course of disease progression.

Concerning SSc, progressive pulmonary dysfunction has become the primary concern, following the release of ACE inhibitors for scleroderma renal crisis, of those investigating mortality linked to this disease. Indeed, pulmonary complications have steadily replaced scleroderma renal crisis as the primary cause of SSc-related death with approximately 50% of mortalities resulting from an associated decline in lung function [1]. Current research is focused on identifying underlying visceral involvement in the early stages so that treatment may be initiated in a timely fashion. Pulmonary involvement in SSc ranges from minor parenchymal fibrosis to severe pulmonary hypertension (PH). To complicate matters, PH in SSc can result from the progression of interstitial lung disease (ILD) or develop as an isolated pulmonary arterial hypertension (PAH),

itself a major mortality factor independent of ILD extent [2]. The clinical evaluation of pulmonary hypertension has proven challenging in the SSc population with 20% of connective tissue disease patients having undiagnosed severe PAH [3] and 14% of SSc patients developing severe PH in the face of initial echocardiographic evidence to the contrary [4]. With regard to screening, both the invasive nature of right heart catheterization (RHC) and the lack of echocardiographic sensitivity have led to an exploration of alternative methods for establishing the diagnosis of PH in general populations at risk of such involvement [5-10]. Computed tomography (CT or CAT) has been investigated as a potential screening device capable of simultaneously assessing the degree of parenchymal lung disease and the level of pulmonary arterial pressure (PAP)[6]. Many studies support the use of chest CT in predicting PH [5-9] with some reporting correlation coefficients as high as 0.83 between main pulmonary artery diameter (MPAD) measurements and PAP [8]. With continued research in this field, it has become increasingly evident that this correlation may be substantially altered by the presence of specific comorbidities. For example, pulmonary fibrosis has recently been found to substantially alter the correlation between MPAD and PAP [11, 12].

In light of the recent identification of pulmonary fibrosis as a complicating factor and when considering the heterogeneity of clinical presentation in SSc, it is necessary that the relationship between MPAD and PAP be closely examined in the scleroderma population. Furthermore, all but one previous study [13] have evaluated the utility of the MPAD measurement in mixed populations comprised

of very few SSc patients. This study will be the first to analyze the correlation between MPAD and PAP using a variety of chest CT protocols to access pulmonary involvement in a sample of scleroderma patients. In acknowledgment of the fact that a large number of cases of PAH occur in SSc patients with little to no fibrotic lung involvement and realizing that pulmonary fibrosis, when present, benefits most from early intervention, this study will focus on examining the correlation between MPAD and PAP in patients without the presence of fibrosis on chest CT as well as those with mild to moderate lung disease.

CHAPTER 2

REVIEW OF LITERATURE

2.1 SYSTEMIC SCLEROSIS OVERVIEW

Systemic Sclerosis (SSc) is an autoimmune disease characterized by widespread mesenchymal cell activation that results in substantial extracellular matrix deposition and fibrosis throughout the body [14]. This disease is notoriously complex with an etiology that remains unclear. Dermal thickening, a.k.a. scleroderma, is seen in the vast majority of SSc cases. Visceral effects are also common and such involvement can progress on a subclinical level for many years [15]. Historically, visceral involvement in SSc has centered around the heart, lungs, kidneys, and gastrointestinal tract. Renal complications account for the majority of SSc-related deaths in the literature predating the release of ACE inhibitors [16-18]. This paradigm has since shifted with pulmonary complications now accounting for approximately 50% of deaths resulting from SSc [1]. With a wide range of potential organ involvement, patient prognosis in SSc is difficult to predict. Therefore, a significant body of literature has been devoted to arranging patients into symptomatically uniform groups for the purpose of establishing accurate prognostic models.

In order to standardize the classification of SSc patients for research purposes, the American College of Rheumatology (ACR) adopted several criteria in 1980 that address the most common manifestations of this disease [19]. Using this system, the classification of suspected SSc cases depends on the

identification of either one major criterion or two minor criteria from a list of multiple disease characteristics. This classification allows patients being evaluated for SSc to be listed as either "definite" or "probable" regarding their disease status and comparisons between patient populations in the literature can be made using this system. A subclassification scheme has been proposed [14] based on the extent of cutaneous involvement and is commonly used in the clinic. The two main subtypes of SSc are limited cutaneous scleroderma (lcSSc) and diffuse cutaneous scleroderma (dcSSc). This model has been shown to define groups with significantly different prognoses. The study that led to this classification scheme incorporated data from SSc patients in whom twelve year survival for diffuse and limited scleroderma was 15% and 50% respectively [20]. More recently, Ferri et al. [15] have demonstrated a similar trend, though somewhat less in magnitude. In their study of Italian patients, the authors report a ten year survival of 75% in lcSSc, a significant difference from the 53% survival seen in the diffuse subtype [15]. Other factors such as seriologic profile and organ involvement, especially the lung, may also be associated with SSc cutaneous subtype [15, 17, 20-22].

As mentioned earlier, pulmonary involvement has become the primary cause of death in SSc and much effort has been devoted to uncovering the nature of this involvement across different scleroderma subtypes. The remainder of this review will be largely devoted to a discussion of the pulmonary complications seen in SSc. The use of computed tomography (CT) in this population as a non-invasive tool, potentially capable of assessing the degree of

interstitial lung disease (ILD) in a given patient as well as identifying those subjects who may benefit from further evaluation for pulmonary hypertension (PH), will also be reviewed.

2.2 PULMONARY INVOLVEMENT IN SYSTEMIC SCLEROSIS

2.2.1 Interstitial Lung Disease

Bounded on either side by basement membrane, the interstitial compartment of the lung may become pathologically altered as the result of over 150 different stimuli [23]. Interstitial lung disease is the name given to the wide range of such alterations originating within this compartment. Lung biopsy, bronchoalveolar lavage (BAL), pulmonary function testing (PFT), and CT are all methods currently utilized by clinicians to confirm the presence of ILD, with biopsy and subsequent pathologic evaluation being the gold standard for this diagnosis. Various histological patterns exist depending on the degree and distribution of inflammatory cell infiltration and fibrosis throughout the interstitium.

Though originally considered to exclusively resemble a histopathological type of ILD known as usual interstitial pneumonia (UIP) [24], it has since been shown that pulmonary interstitial involvement in SSc frequently incorporates features of non-specific interstitial pneumonia (NSIP) [25]. In idiopathic pulmonary fibrosis (IPF), a disease classically characterized by the former histopathological pattern, patients with UIP demonstrate diminished survival when compared to those with NSIP [26]. In addition, a better prognosis has been linked with SSc-associated ILD in past studies [27, 28] when compared to patients with IPF. Therefore, it may be expected that SSc patients with UIP will have a worse prognosis than those with a predominately NSIP pattern of ILD. Bouros et al. [29] have demonstrated, however, that 10-year survival in SSc patients with NSIP did not differ significantly from those with UIP upon retrospective study. In fact, they found that survival depended on initial

physiologic measures taken from PFTs rather than histopathology [29]. As this finding contradicts that seen in IPF [26], the prognostic significance of histological typing in SSc-related ILD remains uncertain.

In contrast to biopsy and pathologic examination, pulmonary function testing is a non-invasive and easily performed clinical assessment regularly used to detect the presence of ILD in SSc patients as well as monitor disease progression. Forced vital capacity (FVC) is one measure derived from PFTs that is widely used to evaluate the restrictive lung defect generated by SSc-related ILD. In a study by Steen et al. [30], lower values of FVC were associated with a decreased cumulative 10-year survival rate. Risk factors for severe restrictive lung disease in SSc include African American race and the diffuse cutaneous subtype [30]. Such factors may be related to a greater extent of inflammatory and fibrotic lung involvement in as much as FVC correlates with the severity of interstitial disease. Yet, as discussed below, FVC is only weakly associated with the extent of disease on CT and may not provide an accurate estimate of total interstitial lung involvement in SSc.

2.2.2 Pulmonary Hypertension

Pulmonary hypertension (PH) is a disorder characterized by elevated pulmonary arterial pressure (PAP) often leading to dyspnea and eventual right heart failure. In SSc, PH can result from the compression of capillaries due to progressive ILD, develop as an isolated pulmonary arterial hypertension (PAH) in which proliferation of the vascular wall leads to occlusion, or emerge as a

combination of these two processes. In a Canadian multicenter study [31] where 29% of patients were found to have elevated PAP, 54.8% had isolated PAH while 29.8% had PH secondary to ILD. In contrast, Launay et al. [32] found a prevalence of 18.3% for moderate to severe PH in SSc, regardless of the presence or absence of significant restrictive lung disease defined as an FVC < 70% predicted. Risk factors for the development of PH in SSc include Raynaud's phenomenon that precedes skin manifestations by at least 3 years, FVC < 80% predicted, and fibrosis on high resolution chest CT [33]. The limited cutaneous subtype of SSc is associated with rapid progression of PH [21].

The screening of SSc patients for PH is an essential practice. Indeed, there is a propensity for elevated PAP to go unnoticed for many years in this population. For instance, Wigley et al. [3] uncovered a large group of patients, 13.3% of those studied, from 50 separate community rheumatology clinics with PAH that had gone previously undetected. Perhaps more importantly, it has been shown in dcSSc-related ILD that PAH is an independent predictor of mortality [2]. While PFTs are often ordered when screening for PH, echocardiography and CT may be more suitable for this purpose. Carbon monoxide diffusing capacity (DL_{CO}) has been explored as a possible functional correlate of PH [34-36] with conflicting results. A study by Mukerjee et al. [34] found a very weak correlation between DL_{CO} and PAP. The tricuspid gradient (TG) on echocardiography exhibited a much stronger correlation with PAP [34] and has recently been incorporated into a composite index along with the CT-derived measurement of main pulmonary artery diameter (MPAD) to screen for

PH [13]. Much of the remainder of this review will be devoted to a discussion concerning the utility of CT in evaluating PH.

2.2.3 Computed Tomography

In the SSc population, CT is widely employed as part of a complete workup of scleroderma lung disease. Aside from biopsy, computed tomography is the only means by which clinicians can directly visualize the inflammation and fibrosis within the lung. It is now standard practice for SSc patients to be evaluated using CT if dyspnea or abnormal PFTs are present. High resolution computed tomography (HRCT) has replaced conventional CT protocols as the gold standard for diagnosis of SSc-related ILD. The main difference between HRCT and conventional CT is the thickness of the slice of tissue being imaged by the scanner [37]. Increased distance between slices is also typical of HRCT protocols, making this imaging technique most suitable for diffuse lung disease such as that seen in SSc [37]. Multiple protocols [11, 38, 39] exist to quantify the extent of ILD on chest CT images. In general, most protocols grade interstitial involvement based on the amount of ground glass opacity (GGO), reticulation, and/or honeycombing appearing throughout the lung. Pulmonary function has been shown to correlate weakly with the extent of abnormality on chest CT [39-41]. This finding suggests that PFTs alone are insufficient for monitoring the natural course of ILD in SSc. Thus, HRCT is essential not only for the evaluation of early disease, but also for tracking disease progression and response to treatment.

Aside from the utility of CT in detecting underlying ILD, this form of imaging has also been the topic of much research [5, 7, 8, 10-12, 42] regarding the evaluation of PH. The pulmonary artery is easily visualized as it passes over the base of the heart on axial CT images and the measurement of MPAD has been found to correlate nicely with PAP [5, 7, 8]. Many of the studies which have examined this relationship have done so in groups of patients with an array of cardiopulmonary diagnoses. Only two studies [13, 36] have looked at the correlation between MPAD and measures of PH in SSc. While Pandey et al. [36] found MPAD to correlate with peak PAP on echocardiography, they concluded that CT-derived fibrosis score was a stronger determinant of PAP. Condliffe et al. [13] evaluated the relationship between MPAD and PAP measured by right heart catheterization in SSc and reported a correlation coefficient of 0.35. This correlation was stronger ($r = 0.57$) when excluding those patients with significant ILD defined as FVC < 70% predicted or extent of lung involvement > 20% on chest CT [13]. Similarly, prior studies in IPF [11] and generalized populations with pulmonary disease [12, 42] have suggested that pulmonary fibrosis attenuates the correlation between MPAD and PAP. The methods used by Condliffe et al. [13] to exclude patients with significant ILD, however, leave several questions unanswered regarding this observation. For instance, do PFT results and disease extent on HRCT equally affect the correlation between MPAD and PAP? Also, do patients with mild to moderate ILD show the same attenuation in the correlation coefficient? Continued research in this area may

reveal the answer to these questions and help further identify the role of CT in the assessment on SSc-related lung disease.

CHAPTER 3

MANUSCRIPT

Relationship of Main Pulmonary Artery Diameter to Pulmonary Arterial Pressure in Scleroderma Patients with and without Mild to Moderate Interstitial Fibrosis

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3.1 ABSTRACT

Purpose: To determine the validity of main pulmonary artery diameter (MPAD) as a marker of pulmonary hypertension in scleroderma patients with and without interstitial lung disease (ILD).

Materials and Methods: We cross-referenced the radiologic database with medical records to identify patients with both computed tomography (CT) scans of the chest and right-heart catheterization separated by no more than six months. Computed tomography scans were reviewed to determine MPAD and extent of ILD for each patient. Ground glass opacity and fibrosis were individually scored by a single thoracic radiologist on a five-point scale. The same radiologist also determined the quality of delineation for the great vessels. MPAD was calculated based on the average of measurements taken from two separate observers. Mean pulmonary arterial pressures (mPAP) were determined by RHC. Patients were divided into either group A (n = 20) or group B (n = 27) based on the absence or presence of interstitial fibrosis respectively. Patients with available data from pulmonary function tests (PFTs) were divided into those with FVC > 70% predicted (Group C) and those with FVC $\leq$ 70% predicted (Group D). Groups were compared using either the Student t test or Mann-Whitney U test depending on the distribution of each variable under consideration. Either the Pearson correlation coefficient or the Spearman rank-correlation coefficient was calculated for each group to evaluate the relationship between MPAD and mPAP.

Results: Groups A and B were similar with regard to MPAD ($p = 0.28$) and mPAP ($p = 0.34$) upon Mann-Whitney U testing. MPAD was strongly correlated with mPAP in both Group A ($r = 0.68$, $p = 0.001$) and Group B ($r = 0.70$, $p < 0.0001$). The correlation between MPAD and mPAP in Group C ($r = 0.69$, $p = 0.002$) was substantially higher than that in Group D ($r = 0.42$, $p = 0.11$).

Conclusion: In our patient sample with scleroderma, MPAD is strongly correlated with mPAP and may indicate the development of pulmonary hypertension regardless of the presence of mild to moderate interstitial fibrosis. An increase in the severity of restrictive lung disease as measured by FVC appears to attenuate the correlation between MPAD and mPAP.

3.2 INTRODUCTION

Progressive pulmonary dysfunction has become the primary concern, following the release of ACE inhibitors for scleroderma renal crisis, of those investigating mortality linked to Systemic Sclerosis (SSc). Indeed, pulmonary complications have steadily replaced scleroderma renal crisis as the primary cause of SSc-related death with approximately 50% of mortalities resulting from an associated decline in lung function [1]. Pulmonary involvement in SSc ranges from minor parenchymal fibrosis to severe pulmonary hypertension (PH). To complicate matters, PH in SSc can result from the progression of interstitial lung disease (ILD) or develop as an isolated pulmonary arterial hypertension (PAH), itself a major mortality factor independent of ILD extent [2]. The clinical evaluation of pulmonary hypertension has proven challenging in the SSc population with 20% of connective tissue disease patients having undiagnosed severe PAH [3] and 14% of SSc patients developing severe PH in the face of initial echocardiographic evidence to the contrary [4].

With regard to screening, both the invasive nature of right heart catheterization (RHC) and the lack of echocardiographic sensitivity have led to an exploration of alternative methods for establishing the diagnosis of PH in general populations at risk of such involvement [5-10]. Computed tomography (CT or CAT) has been investigated as a potential screening device capable of simultaneously assessing the degree of parenchymal lung disease and the level of pulmonary arterial pressure (PAP) [6]. Many studies support the use of chest CT in predicting PH [5-9] with some reporting correlation coefficients as high as

0.83 between main pulmonary artery diameter (MPAD) measurements and PAP [8]. With continued research in this field, it has become increasingly evident that this correlation may be substantially altered by the presence of specific comorbidities. For example, pulmonary fibrosis has recently been found to substantially alter the correlation between MPAD and PAP [11, 12].

In light of the recent identification of pulmonary fibrosis as a complicating factor and when considering the heterogeneity of clinical presentation in SSc, it is necessary that the relationship between MPAD and PAP be closely examined in the scleroderma population. Furthermore, all but one previous study [13] have evaluated the utility of the MPAD measurement in mixed populations comprised of very few SSc patients. This study will be the first to analyze the correlation between MPAD and PAP using a variety of chest CT protocols to access pulmonary involvement in a sample of scleroderma patients. In acknowledgment of the fact that a large number of cases of PAH occur in SSc patients with little to no fibrotic lung involvement and realizing that pulmonary fibrosis, when present, benefits most from early intervention, this study will focus on examining the correlation between MPAD and PAP in patients without the presence of fibrosis on chest CT as well as those with mild to moderate lung disease.

3.3 METHODS

3.3.1 Patient Selection

This study was a retrospective review of patient records and chest CT images contained electronically at our institution. Institutional review board approval as well as an informed patient consent waiver was obtained in order to conduct this research. To be eligible for the study, patients were required to have undergone both RHC and chest CT scan within a designated five year period between November 18, 2003 and November 18, 2008. Additionally, no more than six months was allowed between RHC and chest CT for patients to be included. In the event that a patient had multiple RHCs over the five year period indicated above, only the earliest RHC for which corresponding chest CT data was available was included in the study. A single rheumatology fellow performed electronic chart review to identify those patients meeting the American College of Rheumatology (ACR) criteria for the diagnosis of SSc [19]. Exclusions were made for patients whose chest CT showed signs of intubation or lung resection, whose mediastinal vascular delineation was judged as poor or worse (See CT Scoring Section), who had an insufficient number of image levels to determine overall inflammatory and fibrotic lung involvement, and who received nitric oxide prior to RHC.

For purposes of analysis, patients were divided into two groups based on the absence (Group A) or presence (Group B) of interstitial fibrosis on chest CT (see below). A subset of patients with available pulmonary function tests (PFTs) were also divided into groups based on forced vital capacity (FVC) measurements. To be included in this subgroup analysis, patients were required

to have PFTs within 3 months of chest CT. Patients with FVC > 70% predicted (Group C) were compared to those with FVC ≤ 70 predicted (Group D)

3.3.2 CT Scoring

All CT images incorporated into this study were initially reviewed by one observer (J.R., with 15 years of radiologic experience) to determine the extent of ILD. The same observer also graded each image according to the quality of mediastinal vascular delineation. The extent of ILD was measured according to a previously reported protocol [38] with slight variations. Ground glass opacity (GGO) was evaluated using a six point scale (0 = absent, 1 = less than 5% of total lung, 2 = up to 25% of total lung, 3 = 25% to 49% of total lung, 4 = 50% to 75% of total lung, 5 = greater than 75% of total lung) as was interstitial fibrosis (0 = absent, 1 = interlobular septal thickening w/o honeycombing, 2 = honeycombing involving up to 25% of total lung, 3 = honeycombing involving from 25% to 49% of total lung, 4 = honeycombing involving from 50% to 75% of total lung, 5 = honeycombing involving greater than 75% of total lung). Vascular delineation was rated using a Likert scale (1 = very poor, 2 = poor, 3 = reasonable, 4 = good, 5 = very good)[7].

After eliminating all studies receiving a vascular delineation rating of less than "reasonable", two observers (M.K. and L.H.) independently reviewed the remaining images to measure the diameter of both the main pulmonary artery and the aorta. Measurements were made using computer calipers with both observers blinded to all clinical data regarding the research subjects. All images

were viewed at mediastinal window settings (window width = 390 HU, window level = 60 HU) with the mediastinum zoomed to full screen. The MPAD was defined as the greatest distance perpendicular to the long axis of the vessel as it passes anteroposteriorly across the base of the heart on supine full-chest sequence. The widest diameter of the aorta was also measured at the same scan level.

3.3.3 Right Heart Catheterization

In general, RHC was performed following the acquisition of right femoral vein access using a 7 French introducer sheath. A 7 French Swan-Ganz balloon tipped catheter was then introduced via the sheath and advanced through the right heart chambers into the pulmonary capillary wedge position. PAPs and pulmonary capillary wedge (PCW) pressures were recorded at rest for all patients. Pulmonary vascular resistance (PVR) was calculated using the following equation: PVR = (mPAP-mPCW)/CO where mPAP is the mean pulmonary artery pressure, mPCW is the mean pulmonary capillary wedge pressure, and CO is the cardiac output measured by either Fick's method or thermodilution.

3.3.4 Statistical Analysis

Categorical data are expressed as proportions while continuous variables are characterized by mean (S.D.) if normally distributed or median (range) if distributed otherwise. For continuous variables, comparisons between groups

were made using the Student's t-test or Mann-Whitney U test depending on the distribution of the data. Either the Chi-square test or Fisher's exact test was used to compare categorical data between groups. Correlations were examined using Pearson's coefficient for normal data and Spearman's coefficient if the assumption of normality could not be upheld. Given the limited sample size in this study, four of the following variables were chosen for incorporation into a multivariable linear regression model of mPAP based on the highest univariate correlations: age, gender, ethnicity, aortic diameter, body surface area, and presence or absence of fibrosis on chest CT. In order to investigate any potential interaction regarding the presence of interstitial fibrosis on chest CT and the relationship between mPAP and MPAD, a separate term was incorporated into the multivariable regression model. Receiver operating characteristic analysis was performed to determine the diagnostic accuracy of the MPAD measurement in predicting the presence of PH.

3.4 RESULTS

3.4.1 Patient attributes

After screening our patient base for the previously specified inclusion and exclusion criteria, 48 subjects remained for incorporation into this study. Table 1 contains demographic information as well as clinical data for Group A and Group B. Data was available on a fraction of the patients with regard to several variables including PFT results. Of the 48 patients with suspected scleroderma, 3 patients had undetermined connective tissue disease (UCTD), 1 patient had mixed sine scleroderma /sarcoidosis, 37 patients met the ACR criteria for the diagnosis of SSc, 2 patients met ACR criteria for SSc while also suffering from concomitant lupus, and 5 patients had insufficient records to accurately determine a diagnosis. No significant difference existed between Group A and Group B when considering CT-determined measurements of the mediastinal vasculature and invasive measures of pulmonary hemodynamics. The average MPAD in Group A was 31.3mm (S.D. 4.2mm) compared to 33.2mm (S.D. 4.6mm) in Group B ($p = 0.15$). Upon evaluation of pulmonary hemodynamics, the average mPAP was found to be 27.5mmHg (C.I. 22.4-33.9mmHg) in Group A and 30.9mmHg (C.I. 26.9-35.5mmHg) in Group B ($p = 0.35$). Forced vital capacity data was available in 14 patients from Group A and 20 patients from Group B with mean values of 85.9% predicted (S.D. 19.8% predicted) and 64.2% predicted (S.D. 16.7% predicted) respectively ($p = 0.002$). Diffusion capacity for carbon monoxide (DL_{CO}) was also available in 14 patients in Group A, but only 19 patients in Group B. Similar to FVC, a statistically significant difference in DL_{CO} was found between the groups with Group A having a mean value of 50.1%

predicted (C.I. 43.7-58.9% predicted) and Group B having a mean value of 33.9% predicted (C.I. 28.8-40.7% predicted) ($p = 0.001$).

Overall, 34 patients had available FVC data with Table 2 containing a comparison of important patient characteristics between Group C and Group D. The main differences between FVC-based groups pertain to patient age and MPAD. The average age of patients in Group C was 61.7 years (S.D. 11.7 years) compared to 52.5 years (S.D. 11.3 years) in Group D ($p = 0.03$). On average, MPAD was larger ($p = 0.032$) in Group D (33.0mm, S.D. 3.8mm) versus Group C (30.1mm, S.D. 3.7mm).

3.4.2 Univariate correlations

Strong correlations between mPAP and MPAD were found in this study regardless of the presence or absence of mild to moderate interstitial fibrosis on chest CT (Table 3). The correlation coefficient between mPAP and MPAD in Group A ($r = 0.68$, $p = 0.001$) was very close to the value of the correlation coefficient found in Group B ($r = 0.70$, $p < 0.0001$) (See Figures below). Interestingly, when categorizing patients based on FVC, the correlation between mPAP and MPAD was substantially attenuated with Group C ($r = 0.69$, $p = 0.002$) exhibiting a higher coefficient value than Group D ($r = 0.42$, $p = 0.11$) (See Figures below). Significant correlations were also present in both Group A ($r = 0.50$, $p = 0.03$) and Group B ($r = 0.47$, $p = 0.01$) between mPAP and the ratio of MPAD to aortic diameter (AD), though these values were somewhat less in magnitude when compared to the correlation between mPAP and MPAD. In

contrast, marked variation between Group A ($r = 0.51$, $p = 0.03$) and Group B ($r = 0.09$, $p = 0.67$) can be seen when PVR is correlated with MPAD/AD. This difference is lessened considerably when evaluating the relationship between PVR and MPAD. When the relationship between mPAP and MPAD/AD was evaluated in Group C and Group D, a different pattern emerged than that seen when dividing patients based on CT measurements of interstitial fibrosis. While the correlation in Group C ($r = 0.66$, $p = 0.003$) remained similar to that seen between mPAP and MPAD, Group D ($r = -0.09$, $p = 0.73$) showed no significant correlation between mPAP and MPAD/AD. Group differences in the correlation between invasive measures of pulmonary hemodynamics and PFT results can also be appreciated from Table 3.

3.4.3 Multivariable linear regression

No relationship between mPAP and ethnicity, AD, or fibrosis group was identified on multivariable linear regression with MPAD serving as the primary measure of vascular dimension. Also, there was no interaction between MPAD and the presence or absence of fibrosis using this model ($\beta^{hat} = 0.07$, $p = 0.43$).

3.4.4 Diagnostic Accuracy

Utility of the MPAD measurement was accessed by generating a receiver operating characteristic curve (See Figure below) and calculating the area under the curve (AUC = 0.86). An MPAD value of 30.8 mm yielded the highest sensitivity and specificity at 81.3% and 87.5% respectively.

3.5 DISCUSSION

Frequently incorporated into the assessment of patients at risk for PH, MPAD has been valued by both radiologist and clinicians as an important indicator of elevated PAP with one study reporting a correlation coefficient as high as 0.83 [8] between these two measures. Recent literature [11, 12] has begun to challenge the previously identified relationship between mPAP and MPAD in select populations. Devaraj et al. [12] have demonstrated that no correlation exists between mPAP measured by RHC ($mPAP_{RHC}$) and MPAD in a generalized population of patients suffering from diffuse pulmonary fibrosis. This finding was initially reported in a more specific group of idiopathic pulmonary fibrosis patients by Zisman et al. [11]. Perhaps most recently, the correlation between $mPAP_{RHC}$ and MPAD has been evaluated in a limited group of SSc patients with chest CT data gathered strictly under a pulmonary embolism protocol [13]. We sought to further analyze the correlation between $mPAP_{RHC}$ and MPAD in scleroderma patients using a diverse array of chest CT protocols.

The single prior study [13] concerning the correlation ($r = 0.35$, $p = 0.002$) between $mPAP_{RHC}$ and MPAD in SSc patients initially evaluated this relationship in a group of 81 patients regardless of the extent of ILD. The authors then excluded patients with significant ILD, defined as either a disease extent > 20% according to a high-resolution CT scoring system set forth by Goh et al. [43] or FVC < 70% predicted on PFTs. The remaining subset of 63 patients exhibited a correlation between $mPAP_{RHC}$ and MPAD ($r = 0.57$, $p < 0.001$) that was noticeably superior to that seen in the original group of 81 patients. While these

results demonstrate that higher levels of ILD attenuate the correlation between $mPAP_{RHC}$ and MPAD, several questions remain unanswered. Which, if any, CT-derived measures of ILD may account for this attenuation in correlation between $mPAP_{RHC}$ and MPAD? Furthermore, what is the stability of this correlation in patients with mild to moderate ILD on chest CT who may benefit most from interventions made early in the course of disease?

One major difference between our study and that by Condliffe et al. [13] is the method by which patients were categorized prior to analysis of the correlation between $mPAP_{RHC}$ and MPAD. GGO is a more frequent finding in SSc than in patients with other types of lung disease such as idiopathic pulmonary fibrosis [44] and was highly prevalent in our sample. It is commonly thought that GGO represents alveolar and interstitial inflammation while a reticular pattern and/or honeycombing is more indicative of fibrosis [45-47]. Among the various radiologic signs of ILD, mainly the interstitial fibrosis score has been shown to correlate, if only weakly, with FVC [39]. With these issues in mind and when considering the fact that the interstitial fibrosis score allowed for a more uniform division of groups, we chose to primarily evaluate the role of this CT-derived measure of ILD with regard to the previously described attenuation in the correlation between $mPAP_{RHC}$ and MPAD. Our results show that the correlation between $mPAP_{RHC}$ and MPAD is maintained despite the presence of mild to moderate interstitial fibrosis on chest CT as represented by a fibrosis score of 3 or less. Indeed, 75% of our patients with fibrosis (Group B) had a score of ≤ 2,

representing the moderate nature of this type of interstitial involvement (data not shown).

Despite the discovery that CT-derived fibrosis score did not influence the correlation between $mPAP_{RHC}$ and MPAD in our sample, an interesting finding resulted when categorizing patients based on available PFT data. Values of FVC $\leq$ 70% predicted were associated with a considerably lower correlation ($r = 0.42$, $p = 0.11$) between $mPAP_{RHC}$ and MPAD than values of FVC > 70% predicted ($r = 0.69$, $p = 0.002$). One possible explanation for this difference in correlation could be that the criterion of FVC $\leq$ 70% predicted selects out patients with a greater extent of disease on chest CT scan [43]. In fact, 37.5% of our population with an FVC $\leq$ 70% predicted also had a fibrosis score of 3. Thus, all but one patient in our study with a fibrosis score of 3 was incorporated into Group D. Notwithstanding this discrepancy in fibrosis score distribution when grouping patients based on FVC, it is unlikely that the increase in CT-measured fibrosis is responsible for the attenuation in correlation between $mPAP_{RHC}$ and MPAD seen in Group D. This is evidenced by the finding that the correlation coefficient between $mPAP_{RHC}$ and MPAD in patients with a fibrosis score of 3 ($r = 0.71$, $p = 0.07$) is relatively strong and trends toward statistical significance in spite of an extremely low sample size (See Figure below). Therefore, to reiterate the finding from above, the appearance of fibrosis involving up to 50% of the lungs on CT does not influence the correlation between $mPAP_{RHC}$ and MPAD in scleroderma patients. The revelation that FVC attenuates this correlation may reflect the relatively weak association between CT-measured pulmonary fibrosis

and clinically available measurements of lung function in this population [39].

Contrary to multiple prior studies [7, 12, 13], we did not find MPAD/AD to strengthen the correlation with $mPAP_{RHC}$ in any group. MPAD/AD was most noticeably inferior to MPAD as a correlate of $mPAP_{RHC}$ in Group D. Group D also exhibited significantly larger MPAD values than Group C with no difference in AD or mPAP between the groups. When combined, these factors point to mediastinal traction [7, 11, 42] as a possible explanation for the poor performance of MPAD/AD in Group D, however, concomitant systemic arterial disease may also contribute as such patients were not excluded from this study.

This study has several limitations including a patient sample that was gathered solely from a tertiary care center. Another major limitation was the lack of available PFT data for 14 of the 48 patients in this study. Therefore, subjects with PFT data may represent a subset of patients with more severe disease. In addition, patients were grouped for analysis based primarily on CT-derived measurements of fibrosis alone. As discussed earlier, this grouping was necessary in order to isolate the contribution of fibrosis to the attenuation in correlation between MPAD and $mPAP_{RHC}$. The interval between RHC and chest CT was another potential limitation to this study, although, up to 9 months between tests has been reported in the literature [12].

In summary, this study suggests that the presence of fibrotic lung disease on chest CT scan does not influence the correlation between $mPAP_{RHC}$ and MPAD in scleroderma patients with mild to moderate degrees of total pulmonary involvement. On the other hand, categorizing patients according to FVC may

identify those in whom MPAD is a poor predictor of $mPAP_{RHC}$. Currently available clinical algorithms, such as that proposed by Goh et al. [43] and further exploited by Condliffe et al.[13], may be useful for predicting overall morbidity and mortality in SSc, but limited in utility when assessing morbidity related to PH in this complex and protean disease. Algorithms of this nature may be excessively stringent if used to evaluate suspected PH, thereby resulting in the avoidance of MPAD measurements from patients with higher levels of pulmonary fibrosis on chest CT. Finally, with a positive predictive value approaching 93% in this study, the measurement of MPAD on chest CT may hold future promise in avoiding unnecessary RHC and contribute to PH screening when incorporated in composite scoring systems [13] that enhance the negative predictive value of this measure.

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Table 1: Patient Characteristics by Fibrosis Group

Variable	N(Group A:B)	Total	Group A	Group B	P-value
Age, years	20:28	56.3(13.1)	54.3(13.5)	57.7(12.8)	0.38[¥]
Gender, % female	20:28	81.3	80.0	82.1	1.00*
Race, % caucasian	20:28	68.8	75.0	64.3	0.43[J]
BSA, m^2	20:28	1.8(0.2)	1.8(0.2)	1.8(0.2)	0.53[¥]
ACR, % meeting criteria	18:25	90.7	94.4	88.0	0.63*
Limited: Diffuse, %	17:22	66.7: 33.3	64.7: 35.3	68.2: 31.8	0.82[J]
MPAD, mm	20:28	32.4(4.5)	31.3(4.2)	33.2(4.6)	0.15[¥]
AD, mm	20:28	31.4(3.5)	30.6(3.0)	31.9(3.7)	0.17[¥]
$mPAP_{RHC}$, mmHg[π]	20:28	29.5 (26.3-33.1)	27.5 (22.4-33.9)	30.9 (26.9-35.5)	0.3[¥]
PH, % with mPAP ≥ 25	20:28	66.7	65.0	67.9	0.84[J]
PCW_{RHC}, mmHg	20:28	10(3-35)	9.5(3-17)	11.5(4-35)	0.17[€]
PAH, % of mPAP ≥ 25 with PCW ≤ 15	13:19	68.8	84.6	57.9	0.14*
PVR_{RHC}, $dyn*s/cm^5$	18:26	288(86.5-1097.5)	166.5(94.2-1097.5)	327.7(86.5-744.6)	0.27[€]
FVC, % predicted	14:20	73.1(20.8)	85.9(19.8)	64.2(16.7)	0.002[¥]
DL_{CO}[π], % predicted	14:19	39.8 (35.5-45.7)	50.1 (43.7-58.9)	33.9 (28.8-40.7)	0.001[¥]

Data analyzed using the following: [¥]Student's t-test, *Fisher's Exact test, [J]Chi-Square, [€]Wilcoxin Rank-Sum
[π]Variable was log-transformed. Data represented as antilog of mean (confidence interval).

Table 2: Patient Characteristics by FVC Group

Variable	Total	Group C	Group D	P-value
Age, years	57.4(12.3)	61.7(11.7)	52.5(11.3)	0.03[¥]
Gender, % female	73.5	77.8	68.8	0.7*
Race, % caucasian	70.6	71.4	70.0	1.00*
BSA, m^2	1.8(0.2)	1.7(0.2)	1.8(0.2)	0.14[¥]
MPAD,mm	31.4(4.0)	30.1(3.7)	33.0(3.8)	0.03[¥]
AD, mm	31.3(3.2)	31.4(3.2)	31.3(3.2)	0.92[¥]
mPAP[π], mmHg	26.9 (23.4-30.2)	24 (20.4-28.8)	29.5 (24.6-36.3)	0.1[¥]

Data analyzed using the following: [¥]Student's t-test, *Fisher's Exact test
[π]Variable was log-transformed. Data represented as antilog of mean (confidence interval).

Table 3: Univariate Correlations

Variables	Group A		Group B		Group C		Group D	
	R	P-value	R	P-value	R	P-value	R	P-value
MPAD								
$mPAP_{RHC}$	0.68	0.001	0.7	<0.0001	0.69	0.001	0.42	0.11
PVR	0.62	0.01	0.49	0.01				
MPAD/AD								
$mPAP_{RHC}$	0.5	0.03	0.47	0.01	0.66	0.003	-0.09	0.73
PVR	0.51	0.03	0.09	0.67				
MPAD/BSA								
$mPAP_{RHC}$	0.45*	0.05	0.59*	0.001				
PVR	0.49	0.04	0.54	0.004				
FVC, % predicted								
$mPAP_{RHC}$	-0.52	0.06	0.1	0.69				
PVR	-0.43	0.16	0.35	0.14				
DL_{CO}^{π}, % predicted								
$mPAP_{RHC}$	-0.63	0.02	-0.08	0.75				
PVR	-0.51	0.09	-0.004	0.99				

$mPAP_{RHC}$ was log-transformed for all univariate correlations.

*Spearman's correlation coefficient.

$^{\pi}$Variable was log-transformed in addition to $mPAP_{RHC}$.

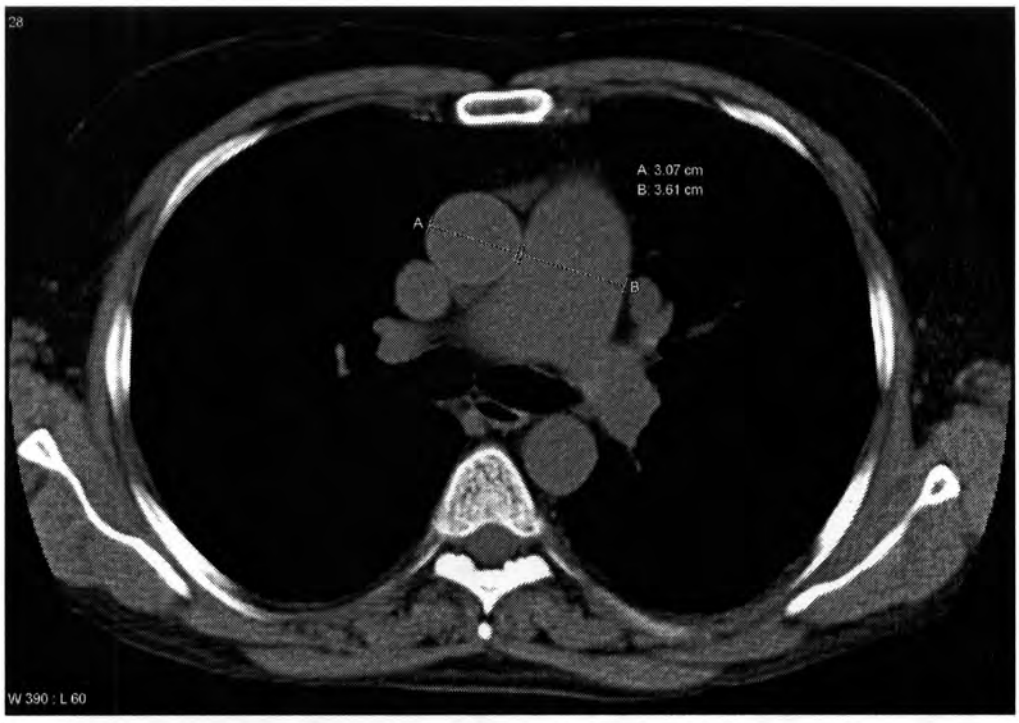

Figure 1: Demonstration of MPAD Measurement on Axial CT Image

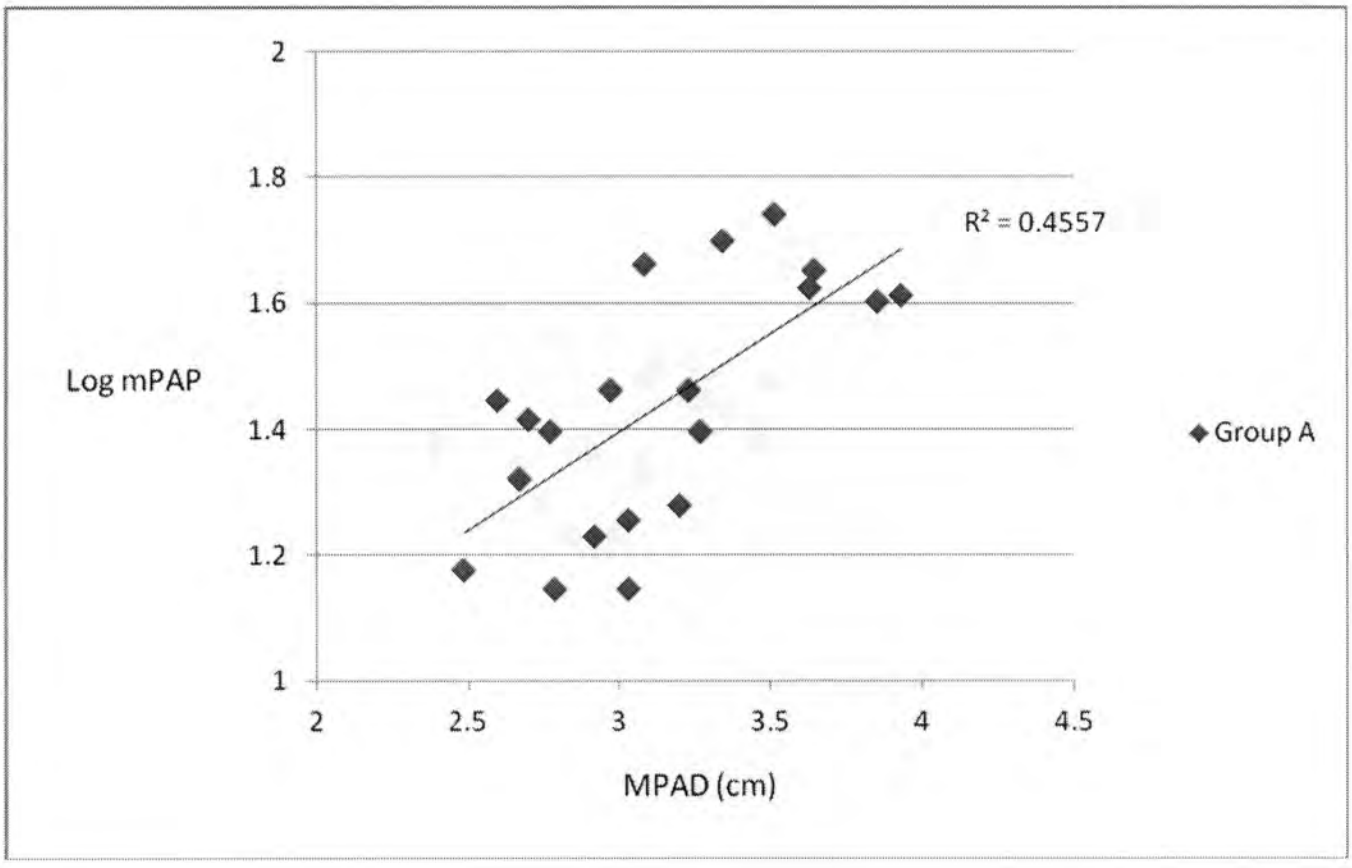

Figure 2: Log mPAP vs. MPAD in Group A

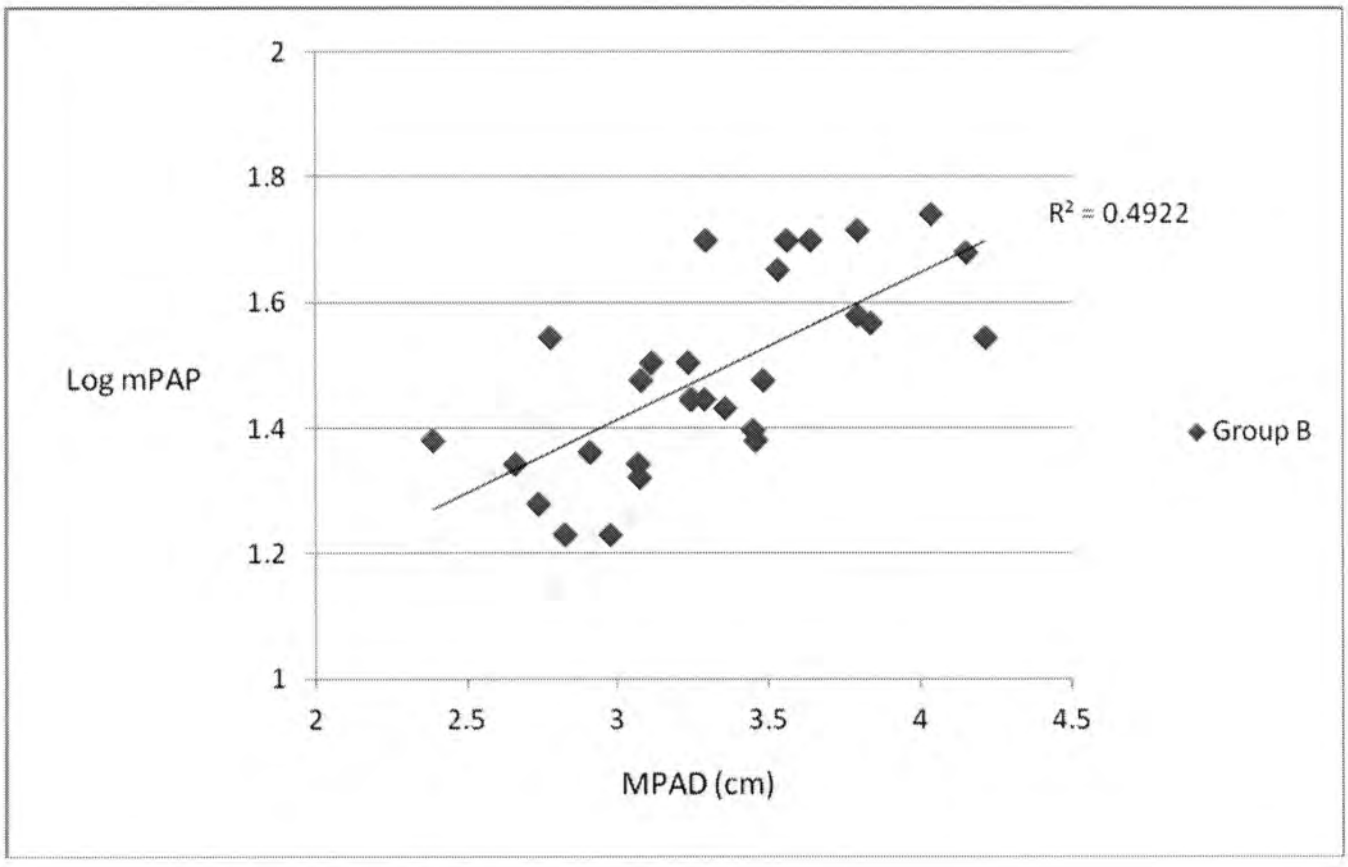

Figure 3: Log mPAP vs. MPAD in Group B

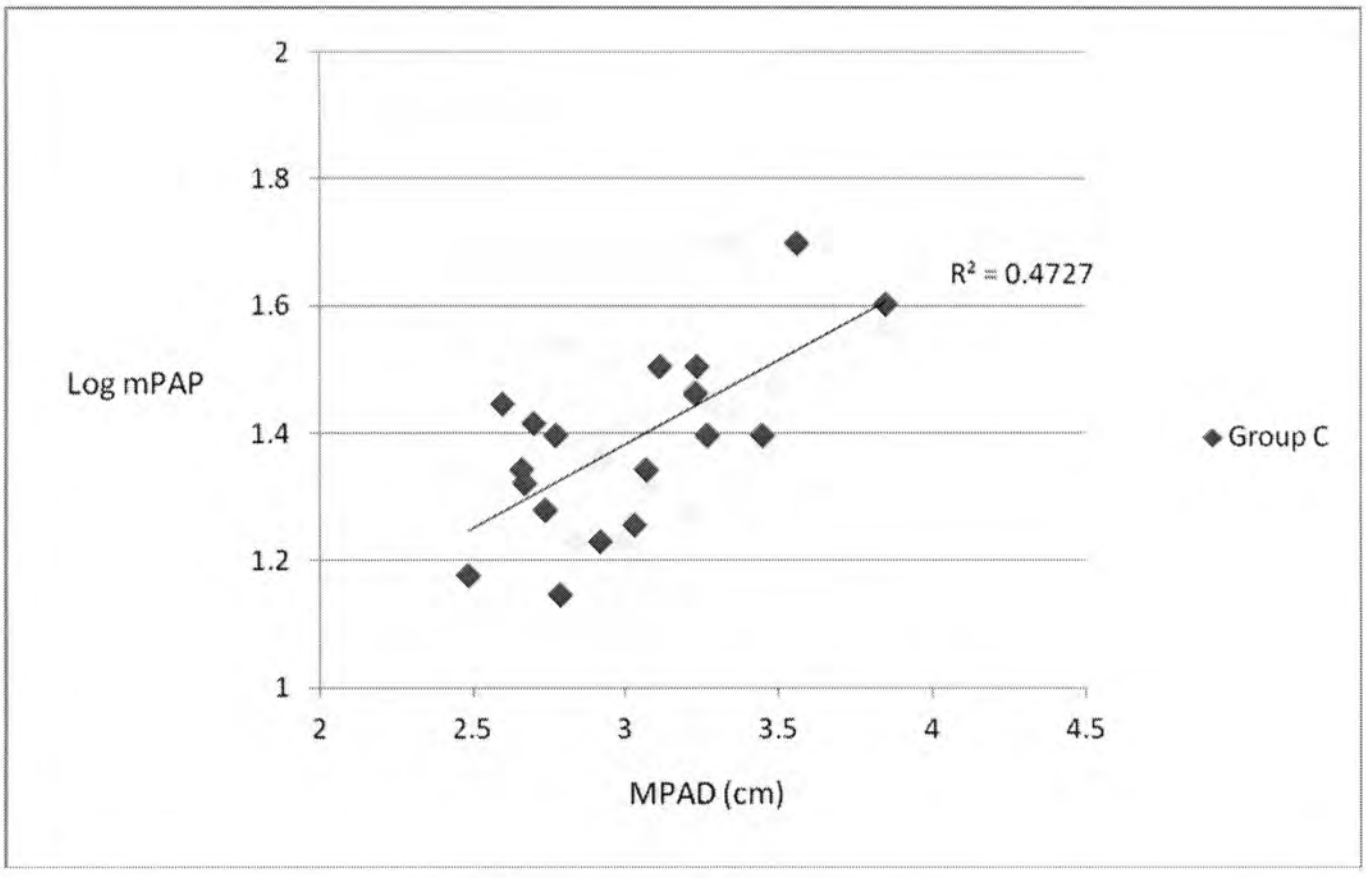

Figure 4: Log mPAP vs. MPAD in Group C

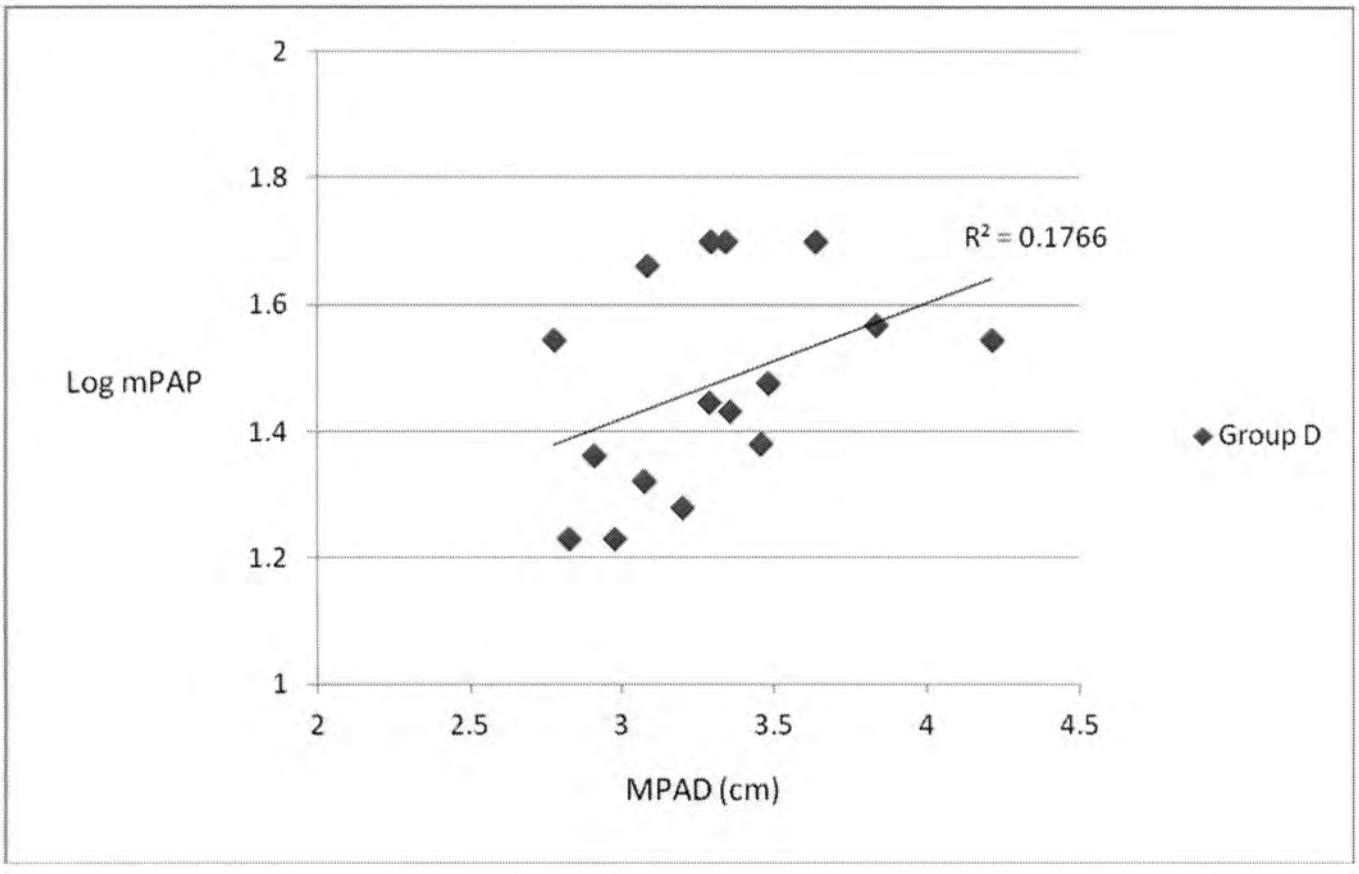

Figure 5: Log mPAP vs. MPAD in Group D

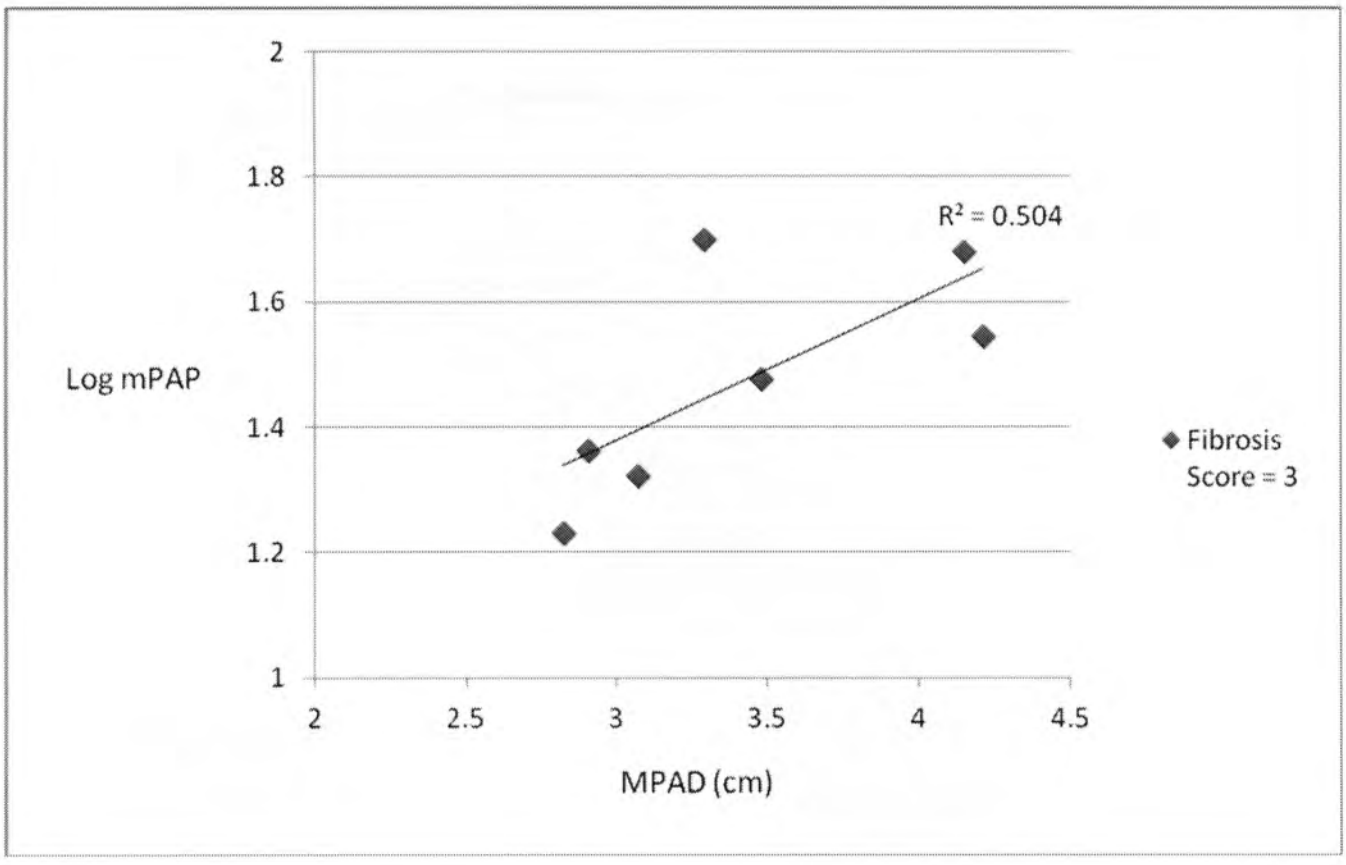

Figure 6: Log mPAP vs. MPAD in Patients with Fibrosis Score of 3

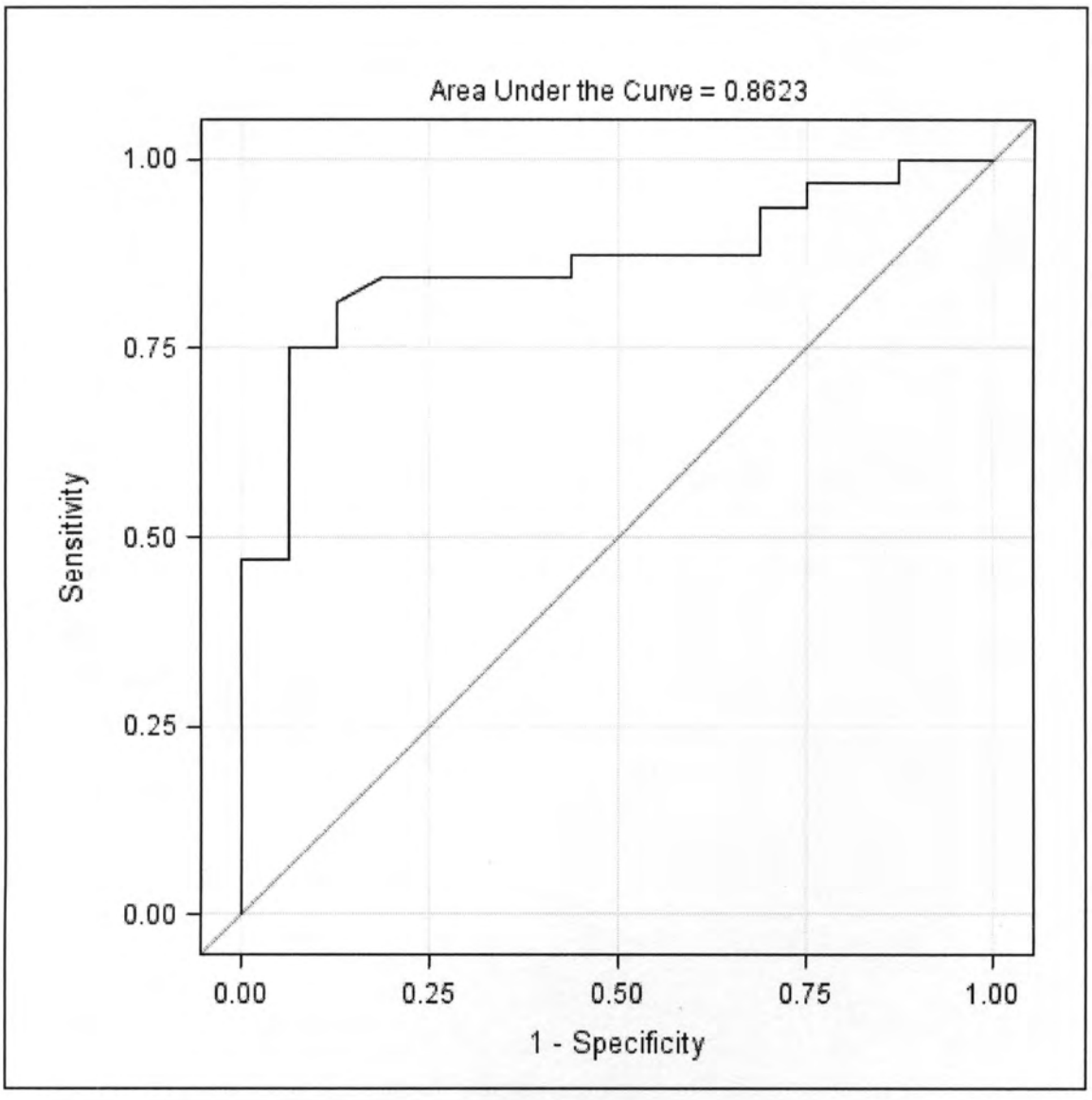

Figure 7: ROC Curve for MPAD Measurement