CHEST Online Supplement

Use of CT Imaging to Quantify Progression and Response to Treatment in Lymphangioleiomyomatosis

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e-Appendix 1.

Methods

Patient Population

This study was approved by the National Heart, Lung, and Blood Institute Institutional Review Board (NHLBI Protocols 95-H-0186 and 96-H-0100). All patients provided written informed consent. Patients were diagnosed with LAM based on American Thoracic Society and/or European Respiratory Society guidelines[1,2].

One hundred thirty-five female patients with LAM (age 49±10 years), who visited the NIH Clinical Center in the last 10 years, participated in a cross-sectional study. For each patient, a HRCT scan and corresponding pulmonary function tests (PFT) were obtained (Table 1).

Thirty-five female LAM patients who were treated with sirolimus (age 45±10.6 years at the start of treatment) were studied in a longitudinal study (Table 1). Two hundred seventy-three HRCT scans and corresponding PFT results, an average of 7.8±2.0 studies per patient, were analyzed. On average, patients were studied for 5.9±3.2 years prior to starting treatment and 4.9±2.3 years after initiating treatment. There was no overlap between the two study populations.

Some of the subjects in this study were also studied in previous reports. 36 of the 38 patients studied in Yao et al (2014)[3] and 13 of the 52 patients studied in Yao et al (2012)[4] are included in this study.

Pulmonary Function Testing

FEV_1 and DL_{CO} were measured using a Master Screen PFT (Erich Jaeger, Wuerzburg, Germany) system per American Thoracic Society/European Respiratory Society standards[5,6]. Testing was performed during the same hospital visit as the CT examination.

Radiologic Methods, Lung Segmentation and Cyst Detection

HRCT scans of the chest (GE Medical Systems, Waukesha, WI; Phillips Healthcare, Amsterdam, Netherlands; Siemens Healthcare, Erlangen, Germany) were performed with the patients in a prone position, as this position minimizes the compression of the lungs by the heart. The radiation dose for obtaining select images of the lungs is over six-fold lower than a standard chest CT with coverage of the chest[7]. The data were obtained prior to the implementation of iterative reconstruction algorithms. Cystic regions and total lung areas were calculated for every slice in a CT examination, yielding a total percent of lung volume occupied by cysts (cyst score) (Figure 1).

Radiologic Methods

HRCT scans of the chest (GE Medical Systems, Waukesha, WI; Phillips Healthcare, Amsterdam, Netherlands; and Siemens Healthcare, Erlangen, Germany) were performed with the patients in a prone

position during end inspiration at 120–140 kilovolt peak and 118–560 mA, with 1- to 2-second scanning times and 34- to 38-cm field of view[4]. Scans
contained 9–13 slices, with slice thickness ranging from 1 to 1.25 mm at 3-cm intervals. Images were reconstructed using a lung kernel (filter) to emphasize the range of pixel values for lung tissues. The prone position minimizes compression of the lungs by the heart. The radiation dose for obtaining select images of the lungs is over six-fold lower than a standard chest CT with coverage of the chest[7]. The data from this study were obtained prior to the implementation of iterative reconstruction algorithms.

Lung Segmentation and Cyst Detection

A computer-aided diagnostic system segmented the lungs based on region-growing and dynamic programing[4]. Two seed points were defined in the right and left lung, and then expanded to fill the lung using a region-growing algorithm. A histogram-based technique was used to exclude large blood vessels and bronchi. An adaptive threshold was used to define cystic regions. Cystic regions and total lung areas were calculated for every slice in a CT examination, summed separately, and then divided, yielding a total percent of lung volume occupied by cysts (cyst score) (Figure 1).

Texture Analysis

Texture properties are established mathematical calculations used to quantify the distribution and intensity of pixels in a selected region of an image[8-10]. Twenty-six texture properties, falling under three categories (histogram measures, co-occurrence matrix measures, and run length measures), were calculated for each HRCT (Table 2).

Histogram measures describe the spread of values (mean, variance, standard deviation, etc.) in a figure that plots the frequency of pixels with a certain intensity. There are 6 texture properties in this category (Table 2). Unlike other texture properties, spatial information is not incorporated into the determination of these measures.

Co-occurrence matrix measures are texture properties that calculate how often pairs of pixels with specific intensities occur adjacent to each other (Table 2). There are 9 texture properties in this category, 4 that utilize global measurements, and 5 that utilize separate measurements in the *x* and *y* direction (Table 2).

Run length measures describe the continuity of signal by identifying 'runs', which are strings of pixels with the same intensity in a certain orientation. These texture properties can either emphasize the length of the runs, the intensity (gray level) of the runs, or various combinations of the two parameters. There are 11 texture properties in this category (Table 2).

After cysts are segmented, all regions near cysts (<10 mm) and away from cysts (>10 mm) are selected separately (Figure 1). Each region is in turn subdivided into smaller pixel blocks for texture computation. 16 x 16 pixel blocks, composed of an 8 x 8 pixel central region with 4-pixel margin overlap on each side, were used to compute textures[4]. Textures for individual pixel blocks are then averaged

across the region and across every slice. The difference in texture (absolute value) between regions near and away from cysts was used to measure of the degradation of lung parenchyma around cysts (Figure 1). For example, the values of the texture property energy at least 10 mm away from cysts 5 years prior to sirolimus treatment were not significantly different from textures at the start of treatment despite decline in lung function and increase in cyst score; however, energy values near cysts varied significantly (p=0.004) (Figure 2). All 26 texture properties were examined, and stable areas far from the cysts were found for each. Therefore, texture values at least 10 mm away from cysts served as suitable controls to measure texture changes near cysts. The difference in texture (absolute value) between regions near and away from cysts was used to measure the degradation of lung texture.

Data Analysis and Statistical Methods

Cross-sectional Study. Linear regression of cyst score versus 26 texture properties was computed. Texture properties with significant (p<0.05) correlations with cyst score were identified and analyzed further in the longitudinal study.

Longitudinal Study. Multiple HRCTs and pulmonary function measurements for each patient were plotted over time. Mixed effects models were used to incorporate within-subject and between-subject variability, as well as repeated measures. Yearly rates of change in cyst score, texture properties, FEV_1, and DL_{CO} were calculated using mixed effects models, adjusting for initial values and sirolimus treatment. Unadjusted, other than the initial value of each outcome, associations of pulmonary function (FEV_1 and DL_{CO}) and cyst score against texture properties were also obtained. While factors such as age, body mass index, and race may play a role in texture changes, we did not adjust for them as determining whether these factors play a role in texture changes would probably be best assessed on a much larger cohort of patients. This is an exploratory study with a relatively small number of subjects, which limits our ability to derive meaningful conclusions about multiple factors that could have an effect in a multivariable model. Percent predicted pulmonary function values are already adjusted for age, sex, and body composition.

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e-Table 1. Listing of means and SE before and after sirolimus treatment for PFTs (FEV_1, DL_{CO}), cyst score, and 18 texture properties of 35 patients using mixed effects models. All analyses were adjusted for the initial values of each outcome variable and time of visit. Texture properties were calculated as the absolute difference in texture between regions near cysts and away from cysts.

	Parameter	Pre-treatment		Post-treatment		P-value
		Mean	SE	Mean	SE	
	FEV1 (L)	1.68	0.05	2.15	0.06	<0.00001
	FEV1 (%predicted)	62.35	1.50	76.85	1.72	<0.00001
	DLCO (mL/min/mm Hg)	10.23	0.33	12.94	0.36	<0.00001
	DLCO (%predicted)	48.78	1.39	60.66	1.58	<0.00001
	Cyst Score (%)	25.43	0.79	20.78	0.97	0.00028
Histogram	Mean	58.54	4.33	57.35	5.34	0.86304
	Skewness	0.32	0.02	0.29	0.02	0.21407
	Kurtosis	0.80	0.05	0.59	0.06	0.00330
Co-Occurrence Matrix	Energy	17.12	1.13	12.43	1.32	0.00238
	Inverse Difference	0.21	0.01	0.17	0.01	0.00617
	Entropy	1.16	0.06	0.92	0.07	0.00453
	Sum Entropy	84.12	3.32	70.81	3.96	0.00642
	Difference Entropy	87.24	2.58	77.05	3.11	0.00910
	Sum Average	106.55	6.74	107.72	8.96	0.92889
	Difference Average	6.37	0.50	5.36	0.61	0.20099
Run Length	Short Run Emphasis	0.13	0.01	0.10	0.01	0.00447
	Long Run Emphasis	4.57	0.33	3.17	0.38	0.00115
	Gray Level Nonuniformity	6.90	0.29	6.19	0.35	0.09934
	Run Length Nonuniformity	16.96	1.12	13.35	1.36	0.03775
	Run Percentage	0.047	0.02	0.37	0.03	0.00231
	Low Gray Run Emphasis	0.015	0.01	0.12	0.01	0.04516
	Short Run Low Gray Emphasis	0.02	0.00	0.03	0.00	0.05017
	Long Run Low Gray Emphasis	4.67	0.37	3.00	0.43	0.00077

e-Table 2. Associations of texture properties with FEV_1 in patient visits prior to sirolimus treatment, as well as in all patient visits (including visits when receiving sirolimus treatment), using mixed effects models. The table lists the coefficient estimate for each predictor variable adjusted for initial values of individual outcomes and time of visit.

	Predictor	FEV_1					
		Pre-treatment visits only			All visits		
		Estimate	SE	p-value	Estimate	SE	p-value
	Cyst score	-0.54	0.10	<0.00001	-0.48	0.08	<0.00001
Histogram	Mean	-0.07	0.02	0.00637	-0.07	0.02	0.00008
	Skewness	-5.63	5.51	0.30847	-10.43	4.34	0.01700
	Kurtosis	-1.82	2.21	0.41129	-5.87	1.71	0.00070
Co-Occurrence Matrix	Energy	-0.32	0.09	0.00052	0.40	0.07	<0.00001
	Inverse Difference	-32.60	9.98	0.00141	-41.73	7.78	<0.00001
	Entropy	-5.78	1.69	0.00086	-7.15	1.34	<0.00001
	Sum Entropy	-0.10	0.03	0.00139	-0.12	0.02	<0.00001
	Difference Entropy	-0.11	0.04	0.00321	-0.15	0.03	<0.00001
	Sum Average	-0.02	0.01	0.07036	-0.03	0.01	0.00515
	Difference Average	-0.39	0.20	0.05918	-0.43	0.16	0.00640
Run Length	Short Run Emphasis	-48.93	14.55	0.00103	-63.20	11.61	<0.00001
	Long Run Emphasis	-1.01	0.31	0.00135	-1.38	0.25	<0.00001
	Gray Level Nonuniformity	-0.63	0.34	0.06423	-0.99	0.26	0.00021
	Run Length Nonuniformity	-0.32	0.09	0.00062	-0.35	0.07	<0.00001
	Run Percentage	-15.36	4.14	0.00031	-18.53	3.26	<0.00001
	Low Gray Run Emphasis	-33.69	9.26	0.00040	-36.72	7.36	<0.00001
	Short Run Low Gray Emphasis	171.67	65.220	0.00957	132.03	47.71	0.00612
	Long Run Low Gray Emphasis	-1.022	0.272	0.00026	-1.31	0.22	<0.00001

e-Table 3. Associations of texture properties with DL_{CO} in patient visits prior to sirolimus treatment, as well as in all patient visits (including visits when receiving sirolimus treatment), using mixed effects models. The table lists the coefficient estimate for each predictor variable adjusted for initial values of individual outcomes and time of visit.

	Predictor	DL_{CO}					
		Pre-treatment visits only			All visits		
		Estimate	SE	p-value	Estimate	SE	p-value
	Cyst score	-0.39	0.10	0.00013	-0.41	0.08	<0.00001
Histogram	Mean	-0.04	0.02	0.06568	-0.05	0.01	0.00155
	Skewness	-1.70	4.73	0.71984	-4.59	3.52	0.19404
	Kurtosis	0.21	2.00	0.91830	-3.23	1.51	0.03407
Co-Occurrence Matrix	Energy	-0.24	0.08	0.00281	-0.28	0.06	0.00002
	Inverse Difference	-24.57	8.83	0.00623	-29.89	6.76	0.00001
	Entropy	-4.37	1.50	0.00424	-5.07	1.16	0.00002
	Sum Entropy	-0.07	0.03	0.00830	-0.08	0.02	0.00007
	Difference Entropy	-0.08	0.03	0.01669	-0.10	0.03	0.00008
	Sum Average	-0.01	0.01	0.20176	-0.02	0.01	0.00233
	Difference Average	-0.53	0.17	0.00249	-0.42	0.13	0.00129
Run Length	Short Run Emphasis	-36.73	12.88	0.00508	-44.39	10.12	0.00002
	Long Run Emphasis	-0.79	0.27	0.00445	-0.95	0.22	0.00003
	Gray Level Nonuniformity	-0.45	0.29	0.12456	-0.62	0.22	0.00587
	Run Length Nonuniformity	-0.23	0.08	0.00525	-0.24	0.06	0.00008
	Run Percentage	-11.76	3.69	0.00181	-13.50	2.84	<0.00001
	Low Gray Run Emphasis	-27.88	8.07	0.00075	-28.62	6.12	<0.00001
	Short Run Low Gray Emphasis	63.58	56.04	0.25876	57.14	39.63	0.15070
	Long Run Low Gray Emphasis	-0.82	0.24	0.00079	-0.97	0.20	<0.00001

e-Table 4. Associations of texture properties with cyst score in patient visits prior to sirolimus treatment, as well as in all patient visits (including visits when receiving sirolimus treatment), using mixed effects models. The table lists the coefficient estimate for each predictor variable adjusted for initial values of individual outcomes and time of visit.

	Predictor	Cyst Score					
		Pre-treatment visits only			All visits		
		Estimate	SE	p-value	Estimate	SE	p-value
Histogram	Mean	0.10	0.01	<0.00001	0.11	0.01	<0.00001
	Skewness	9.26	2.89	0.00168	14.48	2.31	<0.00001
	Kurtosis	3.18	1.24	0.01144	4.41	0.92	<0.00001
Co-Occurrence Matrix	Energy	0.47	0.04	<0.00001	0.49	0.04	<0.00001
	Inverse Difference	49.53	4.63	<0.00001	55.53	3.82	<0.00001
	Entropy	8.83	0.77	<0.00001	9.38	0.65	<0.00001
	Sum Entropy	0.16	0.01	<0.00001	0.17	0.01	<0.00001
	Difference Entropy	0.19	0.02	<0.00001	0.21	0.01	<0.0001
	Sum Average	-0.01	0.01	0.22671	0.00	0.001	0.38374
	Difference Average	0.51	0.10	<0.00001	0.44	0.08	<0.00001
Run Length	Short Run Emphasis	75.37	6.62	<0.00001	79.76	5.74	<0.00001
	Long Run Emphasis	1.53	0.14	<0.00001	1.55	0.13	<0.00001
	Gray Level Nonuniformity	1.26	0.16	<0.00001	1.33	0.14	<0.00001
	Run Length Nonuniformity	0.42	0.04	<0.00001	0.47	0.03	<0.00001
	Run Percentage	22.79	1.86	<0.00001	24.11	1.57	<0.00001
	Low Gray Run Emphasis	49.03	3.86	<0.00001	51.13	3.38	<0.00001
	Short Run Low Gray Emphasis	-105.77	33.97	0.00228	-71.69	26.12	0.00653
	Long Run Low Gray Emphasis	1.43	0.12	<0.00001	1.49	0.11	<0.00001