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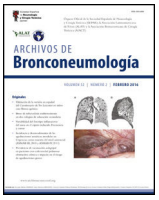

Scientific Letter

Comparing Changes in FDG-PET Activity in Sarcoidosis to Changes in Pulmonary Function Tests

To the Director,

Sarcoidosis is characterized by non-caseating granulomas representing the inflammatory response associated with sarcoidosis. Practice guidelines endorse baseline chest roentgenograms, high resolution computed tomography (HRCT) and pulmonary function studies (PFTs) as part of the initial evaluation[1–3] While integral in the initial evaluation of sarcoidosis, these measures are less sensitive to changes in disease activity. Intuitively, PFTs should track response to treatment, but this relationship has been difficult to validate and demonstrate.[4–6] HRCT scans have only modestly better correlation with lung function.[7]

The inflammation associated with sarcoidosis represents an ideal physiologic measure of disease. Unfortunately, no reliable serum marker exists. Angiotensin converting enzyme (ACE) levels have sensitivity no better than 50%.[8] However, ^{18}F-flourodeoxyglucose (FDG) positron emission tomography (PET) accurately identifies and tracks inflammation in sarcoidosis.[9–11] FDG-PET uptake in sarcoidosis can be increased in fibrotic lung disease, occult sites and also reflects response to treatment. This is seen as decreasing (improvement) or increasing FDG-PET activity (worsening).[12]

Since FDG-PET scans are more sensitive to changes in disease activity, it follows that changes should be mirrored in PFTs. Long term experience with FDG-PET scans in sarcoidosis provided an opportunity to better characterize the relationship between FDG-PET scans and PFTs.

This single center retrospective review is of all patients with sarcoidosis referred to our Pulmonary clinic between 1997 and 2023. All had histologically confirmed sarcoidosis, two FDG-PET scans and two PFTs obtained within four months of either study. FDG-PET scans were obtained at the discretion of the pulmonary physician. Typical indications were to establish a baseline, assess disease activity, response to therapy and guide treatment.

Pulmonary function studies adhered to American Thoracic Society (ATS) guidelines. Forced vital capacity (FVC) values were recorded from plethysmography or spirometry. The pulmonary function systems used were from Sensormedics©, Carefusion© or Vyaire©.

Patients fasted six hours prior to FDG-PET imaging. FDG-PET scans were obtained with either Siemens ECAT-935, GE Discovery ST PET/CT or Phillips Gemini TF64 PET/CT scanner after the injection of 10.4, 11.79 or 7.5 mCi (F^{18}) 2-fluoro-2-deoxy-D-glucose respectively, with images from the skull base to the upper thigh after 60 min of injection. FDG-PET scan results were taken directly from imaging reports. Quantitative standardized uptake values (SUV) were not consistently reported and analysis was based on changes to FDG-PET uptake.

All data were confirmed for accuracy by two authors. Statistical analysis was conducted using MedCalc® statistical software version 20.116, (MedCalc Software Ltd, Brussels, Belgium) using paired samples t tests, Wilcoxon paired samples and comparison of proportions where appropriate. The significance level was 0.05. The study was reviewed and approved by our IRB, deemed low-risk with waiver of informed consent.

Of 143 patients with sarcoidosis and FDG-PET scans since 1997, 90 had at least two FDG-PET scans, and 83 patients met all inclusion criteria. This consisted of 75 males (90%) and 8 females (10%). There were 53 (64%) African-American, 23 (28%) Caucasian/White and 7 (8%) Hispanic. Average age was 55.8 ± 12.7 years (range 32–79 years). Sarcoidosis staging was Scadding stage 0 = 3 (4%), stage I = 17 (20%), stage II = 48 (58%), stage III = 13 (16%) and stage IV = 2 (2%). All subjects had increased FDG-PET uptake, 36 (43%) had extra-thoracic disease, mostly (24/36 = 67%) extra-thoracic nodal involvement. Time between initial and follow-up FDG-PET scans was 18.4 ± 22.7 months, (mean ± SD); (range 3–125); with 28 (34%) by 6 months and 50 (60%) within 12 months.

All had initial and follow-up spirometry (n = 83), but two missed repeat DL_{CO} (N = 81) and seven were without paired lung volumes (N = 76). Half (83/166) were obtained within one month of the FDG-PET scan with 63% (105/166) within two months.

No significant differences were noted between any initial and follow-up PFTs for the entire group or any subgroup. Except for a slight decline (non-significant) in DL_{CO}, the values for total lung capacity (TLC) and FVC were basically flat. In Table 1, section A, for patients with improvement in FDG-PET scan uptake, about 50% had any improvement in lung function. Of 47 patients treated with immunosuppressives, 40 (85%) were treatment naive, getting started based on FDG-PET scan results. All patients received prednisone, and twelve received one additional agent, methotrexate (6), azathioprine (5), infliximab (1). Findings were similar in subgroups treated with immunosuppressives and Scadding stage II-IV disease. In section B, patients with unchanged or worsening FDG-PET scans had minimal differences in PFTs. About half had changes in TLC and FVC with the average change barely 200 ml (TLC) and <100 (FVC). Most (73.3%) had a decreased DL_{CO} (2%). In those with improved FDG-PET scans, only 26.4% had improvement in all three measures (TLC, FVC, DL_{CO}). In unchanging or worsening FDG-PET scans, concordance for all three was 20.0%. This is further illustrated in Fig. 1 where the mean change in all groups hovered around zero.

Pulmonary function studies represent a critical element in sarcoidosis.[1–3] While their role in the evaluation of sarcoidosis is

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Table 1
Section A. Baseline and Follow-Up PFTs, Patients With Improved FDG-PET Scans.

Patients ($N = 47$)	TLC T_1	TLC T_2	Positive Difference	p Value
Mean ± SD	5.54 ± 1.71 L	5.56 ± 1.68 L		0.884
Median (95% CI)	5.35 L (4.77–6.24 L)	5.35 L (5.04–6.09 L)	28/47 (59.6%)	0.310
Percent predicted	85.2 ± 18.7%	85.5 ± 15.1%		0.835
Median (95% CI)	83.0% (75.0–89.7%)	84.0% (78.0–89.0%)	26/47 (55.3%)	0.359
Patients ($N = 53$)	FVC T_1	FVC T_2	Positive Difference	p Value
Mean ± SD	3.52 L ± 1.01 L	3.57 L ± 1.02 L		0.430
Median (95% CI)	3.34 L (3.01–3.88 L)	3.55 L (3.02–3.91 L)	25/53 (47.2%)	0.772
Percent predicted	80.4 ± 19.1%	80.3 ± 17.2%		0.921
Median (95% CI)	79.0% (74.0–86.1%)	80.0% (72.8–86.2%)	26/53(49.1%)	0.899
Patients ($N = 51$)	DL_{CO} T_1	DL_{CO} T_2	Positive Difference	p Value
Mean ± SD	18.47 ± 6.50 m/m/Hg	18.28 ± 6.60 m/m/Hg		0.600
Median (95% CI)	17.40 (15.86–20.21)	18.45 (16.51–19.90)	20/51 (39.2%)	0.481
Percent predicted	65.80 ± 22.00%	65.86 ± 20.6%		0.967
Median (95% CI)	68.0% (60.0–71.0%)	66.1% (60.0–70.0%)	24/51 (47.1%)	0.549

Section B. Baseline and follow-up PFTs, unchanged or worsening FDG-PET

Patients ($N = 29$)	TLC T_1	TLC T_2	Positive Difference	p Value
Mean ± SD	5.82 L ± 1.23 L	5.98 ± 1.30 L		0.259
Median (95% CI)	5.69 L (5.25–6.26 L)	5.86 L (5.18–6.56 L)	15/29 (51.7%)	0.552
Percent predicted	84.8 ± 14.0%	85.1 ± 17.3%		0.884
Median (95% CI)	84% (77.8–88.2%)	84.0% (76.8–88.2.0%)	12/29 (41.4%)	0.489
Patients ($N = 30$)	FVC T_1	FVC T_2	Positive Difference	p Value
Mean ± SD	3.80 L ± 0.91 L	3.77 L ± 0.88 L		0.828
Median (95% CI)	3.77 L (3.36–4.30 L)	3.68 L (3.14–4.32 L)	14/30 (46.7%)	0.680
Percent predicted	80.3 ± 16.5%	80.8 ± 17.8%		0.780
Median (95% CI)	81.0% (72.5–88.8%)	80.0% (71.7–89.8%)	13/30 (43.3%)	0.792
Patients ($N = 30$)	DL_{CO} T_1	DL_{CO} T_2	Negative Difference	p Value
Mean ± SD	21.56 ± 6.89 m/m/Hg	20.46 ± 7.30 m/m/Hg		0.050
Median (95% CI)	21.50 (18.0–24.5)	19.8 (17.8–21.5)	22/30 (73%)	0.034
Percent predicted	72.06 ± 19.59%	70.67 ± 22.38%		0.400
Median (95% CI)	71.5% (67.4–81.7%)	69.5% (58.2–76.0%)	15/30 (50.0%)	0.853

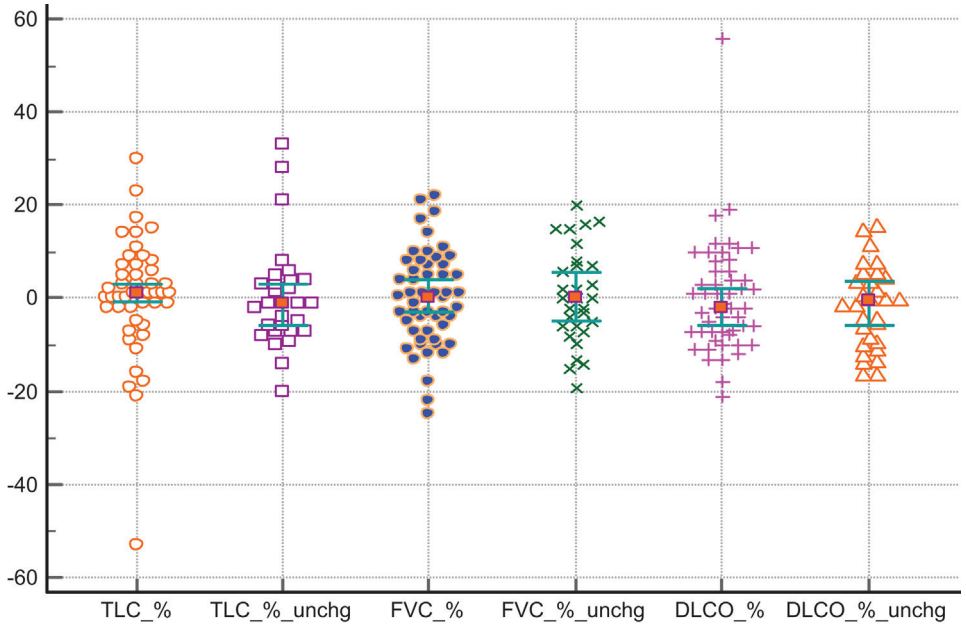

Fig. 1. Change in percent predicted between initial (T_1) and follow-up (T_2) pulmonary function studies in those with improved and unchanged or worsening FDG-PET scan images. No change is represented by zero, improvement by a positive number and decline by a negative number.

undisputed, the experience in monitoring is less robust.[4,5,13,14] Our cohort demonstrated minimal changes and only modest concordance of change in PFTs even when paired to changes in FDG-PET imaging. This is similar to past reports where changes to PFTs occurred in 50–60% of patients or 20% for ALL measured variables (FVC and DL_{CO}) with the majority (~80%) having changes to only one or two measures.[4,13]

In analysis of subgroups in randomized trials, increases of 350 and 220 ml in VC and less than 1 ml/min/kPa for DL_{CO} were noted at 18 months and five years or 3.1% in FVC and 6.3% in DL_{CO} at 18 months.[15] In another review, corticosteroid treated patients had a weighted mean improvement of 4.2% (95% CI: 0.4–7.9%) in FVC and 5.7% (95% CI 1.0–10.5%) in DL_{CO}.[16] Newer measures in sarcoidosis incorporate other outcome variables but still include PFTs.[17]

When compared to PFTs, FDG-PET scans detect inflammation better and exhibit changes not reflected by PFTs. There was only modest correlation, minimal and small magnitude of change in PFTs compared to the changes detected on FDG-PET scans. FDG-PET scans seem to be a more sensitive marker of inflammation in sarcoidosis, but the clinical impact of these changes remains to be determined. Nevertheless, PFTs remain an important outcome variable.[4,13] PFTs are part of all clinical trials where reported changes in PFTs have been similarly modest.[14,15,18] Clinical improvement may not represent much change to PFTs and awaits correlation with changes in FDG-PET uptake. This suggests an increasing role for FDG-PET scans in sarcoidosis. Guidelines acknowledge the use of FDG-PET scans in patients with suspected sarcoidosis but are silent on their role during treatment.[2]

The limitations to our findings are those inherent in a single center cohort study. Other measures of clinical disease activity were not obtained. However, the consistency over time strengthens findings and conclusions. Our experience reinforces the need for composite measures of disease activity as vasculopathy and other manifestations of sarcoidosis are not captured by PFTs or FDG-PET scans alone.[17]

In summary, changes in sarcoidosis detected by FDG-PET scans are not consistently reflected in PFTs. Our results call for further evaluation of FDG-PET scans in sarcoidosis, acknowledging issues with availability, restrictions and reimbursement. On the other hand, FDG-PET scans no longer represent scarce technology and warrants incorporation into multi-center clinical trials.

Authors' Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by all authors. The first draft of the manuscript was written by Guy W. Soo Hoo and all authors commented on all versions of the manuscript. All authors read and approved the final manuscript.

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Conflicts of Interest

The authors have no conflicts of interest, direct or indirect to report.

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Guy W. Soo Hoo [a,b,*], Melisa R. Chang [a,b], Curtis C. Sather [c]

[a] *Pulmonary, Critical Care and Sleep Section, VA Greater Los Angeles Healthcare System, USA*
[b] *David Geffen School of Medicine at UCLA, Los Angeles, CA, USA*
[c] *Pulmonary Medicine; Huntington Health, Pasadena, CA, USA*

[*] Corresponding author.
E-mail address: Guy.soohoo@va.gov (G.W. Soo Hoo).