

APS COVID Webinar: February 24, 2021

X-ray Darkfield Contrast for Improved COVID-19 Detection in Chest X-Rays - Basic Physics & First Clinical Results

Franz and Daniella Pfeiffer, Technical University of Munich

Clinical Introduction

- Early diagnosis of lung disease is crucial
 - #3-5 of diseases with top 5 death rate are lung based (from WHO)
- COPD (>130,000 deaths/yr in US)
 - 2 variations: Bronchitis and emphysema
 - Symptoms = breathing difficulties, cough
 - Typically found in smokers
 - People can suffer over decades, and there are no specific therapies
 - 6% of US adults are affected
 - Use CT to examine lungs because has really good contrast
 - See a change on CT images, destruction of the alveoli
 - Not enough interfaces between air and lung tissue
 - Use x-ray as well
 - See increased diameter of the chest
 - Must be very severe to detect COPD in x-ray
- Lung cancer (>150,000 deaths/year in US)
 - CT-based screening encouraged in US
 - On CT, see a large round mass, typically with small spikes representing spread into the lung tissue
 - It is often easy to find the tumor on x-ray as well
 - Sometimes only looks like a tiny lung nodule on x-ray, though easy to see on CT
- While 2D x-ray is helpful, we are not satisfied with the performance, especially in COPD cases
- COVID-19 (>500,000 deaths in US since 3/2020)
 - Low dose CT typically shows ground glass opacities in both lungs
 - Typically found more in the periphery
 - Literature says it starts with ground glass opacities and consolidates as it advances
 - Harder to see on chest x-rays because of superposition of lots of tissues (until advanced/severe)
- CT vs Chest x-ray
 - Dose comparison: chest CT = 2-4 mSv; x-ray = 20-40 microSv
 - Take more x-rays than CTs due to lower dose, but CTs are more helpful/clear
- That's where phase-contrast and darkfield x-ray imaging comes in!

Physics and technology development

- X-rays are described by phase-shift and attenuation terms (use this phase shift for this technique)
- X-ray phase contrast measures refraction of x-ray waves in the object
 - Uses a reference grating and analyzer grating to measure the phase shift
 - Placement depends on the Talbot effect and type of grating
 - Provides additional contrast which improves sensitivity
- X-ray darkfield contrast

- Measures small angle scattering in the object
- Uses a reference grating and analyzer grating to measure the intensity pattern
- Sensitive to micro-structures in the object
 - Demonstrated in image of cappuccino
- Data processing: Extract the total transmission, refraction signal, and darkfield signal
 - Then separate these effects
- Technique became a big deal just a few years ago
 - First measurements in living animals in 2012
 - Darkfield really highlights the lung (and other microstructures in the mouse)
- Have done several preclinical studies, including COPD-detection in mice
 - See almost no change in conventional x-ray
 - See a consistently reduced attenuation in new technique images
- Preclinical study in lung cancer in mice
 - Showed 244% improvement in lesion detection on chest x-rays
- Preclinical study on pneumonia (similar to COVID-19)
 - One of the mice in the COPD study had a pneumonia-like reaction
 - See modification of tissue structure on darkfield in mouse
- Model for darkfield signal loss with pneumonia
 - Fewer interfaces => less scattering
 - Dry versus drenched sponge: dry measured on darkfield, but invisible on attenuation
- Clinical translation:
 - Large animal darkfield prototype for use on pigs
 - Requires larger FOV and higher energies
 - Show a significant imaging signal in lung of pig for darkfield at high energies, large FOV
 - First measurement of its kind!
 - Now developed a darkfield chest x-ray prototype for patients
 - Started in 2016, patient study in 2019
 - Requires 7 second breath-hold for patients standing vertically in the system
 - Move the scanner up the patient
 - In processing, need to remove movement and vibrations
 - Are able to extract a transmission and darkfield signal
 - Performed extensive phantom studies (had to create own phantoms with cotton)
 - Dose = 35 microSV (delivers both conventional & darkfield image)

Clinical results:

- 33 year old healthy male shows very little differences in conventional x-ray from 73 year old male with severe COPD
 - Comparison of same patients in darkfield imaging shows almost complete loss of darkfield signal in COPD patient – strongly demonstrating the physiological differences of this patient
- Can show difference between healthy, mild COPD, and severe COPD in darkfield
 - No detectable differences in conventional x-ray
 - Mild COPD looks like faded healthy lung signal, helps obtain early diagnosis
- Currently have scanned 96 patients in a 500 patient COPD study (mild to severe)
 - Can sort patients by severity of COPD by differences in darkfield images

- Darkfield x-rays for COVID-19:
 - No obvious signs of COVID visible in conventional x-ray
 - See significant reduction of general darkfield signal in several COVID patients
 - In addition, see dark spots in periphery indicating the ground glass opacities
 - See patches of consolidations on darkfield also as loss of signal (matches patterns in CT)
 - 2 classes of covid patients
 - Generally reduced darkfield signal
 - Patchy reduced darkfield signal

Summary + Outlook

- Darkfield chest x-ray is sensitive to microstructural changes associated with lung diseases
- Can successfully be translated to clinical scale and first patient applications
- Improves early detection of COPD and COVID-19 (wrt plain chest x-rays)
- Has about 100x lower dose than low-dose CT
- Can offer a better screening modality for lung disease patients
- What's next?
 - Publishing COPD results
 - Publishing first COVID-19 results
 - Start new COVID-19 cohort
 - Attempt to discriminate from other lung diseases
 - Developing darkfield CT also
 - Predict to have first results by next year

Question and Answer:

- Is the change in the lungs from COVID-19 permanent or does it revert? How do you see the importance of imaging in the follow up of COVID survivors?
 - In majority of patients, effects are reversible
 - Some patients show what looks like scarring on CT (~30% of patients)
 - Patients sometimes report not feeling back to normal in their lung function
 - We need more time to learn and study these patients (many patients never come back after leaving the hospital)
 - Need a CT to see this, but wouldn't do this for dose concerns if patient feels good
- How quantitative is darkfield imaging?
 - Method is quantitative – measure essentially the number density of interfaces
 - Corresponds to alveoli measurements in histology
- Have you done repeatability studies? Do you have an estimate of the uncertainties in the quantitative features?
 - Haven't done repeatability on patients (presently not included in ethics vote), but have done many phantom measurements (repeat every day)
 - Phantoms have shown constant measurements for ~ a year
 - Have been limited by radiation protection rules to do repeatability
 - More important to do measurements comparing breath hold variations than different days
- Is there a general change in the lung that conventional imaging is not picking up? (in addition to the ground glass opacities)

- Not sure! Didn't expect to see the general reduction in darkfield imaging signal. Don't see this on CT or x-ray... needs more investigation, but is convincing that there is something going on in the whole lung that is not captured by conventional imaging
- Comment further on the sensitivity?
 - In second pilot study, want to explore whether they can distinguish between mild, moderate, and severe covid patients to try to quantify the sensitivity
- Do different diseases produce different patterns? Could you tell a patient that has asymptomatic covid?
 - Not sure yet! Only scanning patients with symptoms
 - Going to study comparison to other diseases in next study
- What do you think is the optimal operating energy for darkfield?
 - From clinical POV, we are operating outside of the guidelines (70 kVp vs 120 kVp, with approval!)
 - Doing this because of the very strong dependence of the energy signals
 - It's also possible that these guidelines need to be updated (were established ~20 years ago)
-