Reimagining emphysema for a computational age

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Emphysema remains an enigma. Visual classification of emphysema on computed tomography (CT) imaging has remained unchanged for over 30 years and essentially constitutes the identification of three disease patterns: centrilobular [1,2], paraseptal [3] or panlobular [4] emphysema. This classification originates from anatomical descriptions dating from the 1950s specifying the location of airspace destruction within the acinus or lobule and the proximity of emphysema to the visceral pleura. The extrapolation of histopathological scale features of damage [5,6] to the clinical CT scale was a key milestone in the early years of lung CT interpretation.

Yet when considering emphysema and its role in disease pathogenesis and progression one is led to wonder what has been lost by only considering emphysema in terms of three anatomical patterns. Centrilobular emphysema can itself comprise a range of imaging phenotypes, from frank destruction of an entire secondary pulmonary lobule to subtle reductions in peribronchiolar lung density that may be easily missed at first glance. Whilst visual evaluation has focussed on measuring emphysema extent, could we be inadequately capturing emphysema severity?

The advent of computer analysis of lung CT imaging dramatically improved the ability with which emphysema extent could be quantified using density masks [7] or parametric response maps [8]. Computer tools typically evaluate the entirety of the lungs in discretised small voxel volume units. Whilst valuable information pertaining to the co-ordinates and morphology of emphysema, and its spatial relationship to the surrounding lung parenchyma is embedded within CT data, this is mostly discarded in the outputs of computer models which quantify emphysema with a single number.

To address existing limitations in emphysema characterisation, in this edition of Thorax, Angelini et al [9] applied a data-driven approach to reclassify pulmonary emphysema subtypes in subjects with COPD. Emphysema detection utilised a -950HU density threshold applied across small lung volumes (25x25x25mm) and importantly considered textural and spatial features within emphysematous regions. Unsupervised clustering resulted in the identification of six emphysema subtypes which were then phenotypically described by chest radiologists after considering pertinent physiological and demographic information.

In three of the six emphysema subgroups: the combined bronchitis-apical, diffuse and vanishing lung groups, the distinctive morphological and anatomical localisation of emphysema conforms well to recollections of COPD CTs reported in routine practice. Two of the other COPD emphysema subtypes were associated with fibrosis (combined fibrosis and emphysema [CPFE]) and are less intuitive. These were termed “Obstructive CPFE” and “Restrictive CPFE” and describe the now increasingly recognised overlap between COPD and fibrosing lung disease. Imaging of these patients is crucial to identify co-existent fibrosis which might be missed if there was reliance on lung function testing alone for diagnosis of COPD and related conditions.

A clear advantage of the approach employed by Angelini et al [9] was a more nuanced consideration of emphysema location beyond centrilobular and paraseptal distributions when classifying emphysema subtypes. The phenotypic description of the emphysema subtypes also considered co-existent bronchial wall thickening and vascular abnormalities, thereby providing a broader context to COPD-related parenchymal damage. Finally, distinct demographic, clinical, functional, genomic, and prognostic associations were identified for some of the various emphysema subtypes.

Reimagining the characterisation of emphysema is a timely endeavour and the study by Angelini et al [9] provides an early template for data-driven image analysis in COPD populations. However, COPD-related damage includes local extents and severities of emphysema, small airways disease, large airways disease, mucus plugging, interstitial fibrosis and vascular and cardiac damage. Future studies should aspire to quantify the spectrum of COPD imaging abnormalities, not just emphysema, and cluster these using unsupervised machine learning techniques [10] to identify important disease subgroups who may show differing patterns of disease progression. As multimodal data becomes increasingly available, disease clusters should also be informed by integration of genetic, environmental, comorbid and host factors which influence exacerbation risk, functional decline and mortality.

Whilst current research studies focus on analysis and validation within COPD databases, lung cancer screening populations might be the ideal cohort in which to study COPD progression and validate quantitative tools. Lung cancer screening programs benefit from a relative abundance of subjects with pre-symptomatic COPD and screening routinely captures

longitudinal imaging, allowing the delineation of early disease evolution and identification of progressive phenotypes. By 2028 it is estimated that almost 1 million subjects in the UK will be screened with CT annually in the national roll out of lung cancer screening [11]. Among the heavy-smoker population invited for lung cancer screening, cohort studies suggest 20-30% will have undiagnosed COPD [12,13] and similar proportions will have no COPD on spirometry.

An era can be envisioned where detailed quantitative reports could help radiologists describe annualised trajectories of various patterns of respiratory and cardiac damage beyond that expected from normal ageing in COPD subgroups. These outputs could be fed into multi-dimensional risk scores which integrate clinical, environmental and genomic data to personalise risk-prediction for progressive disease across disease endotypes. This would have the additional advantage of aiding recruitment of subjects to early disease therapeutic trials for which imaging could provide composite trial endpoints.

Allied to more comprehensive CT quantitation of patterns of damage in COPD, new imaging modalities are also refining our understanding of disease pathophysiology. For example, vascular changes in the lung have been underappreciated in pre-symptomatic and symptomatic COPD. Yet modern non-destructive microstructural imaging of entire ex-vivo lungs now capable with micro-CT [14,15] and hierarchical-phase contrast tomography [16] can delineate previously unknown pulmonary-systemic anastomoses[16]. These techniques are likely to herald a second wave of radiological-pathological correlations as three-dimensional histopathology, achievable with micro-scale imaging of entire lungs, is computationally mapped to and validates patterns of lung damage previously only inferred on clinical CT.

The coming years are likely to result in an expansion of complex machine learning models capable of subgrouping COPD and lung cancer screening patients across a broader range of better defined and quantified anatomical structures. This process may help blur existing distinctions between patients currently diagnosed with COPD, fibrosis and bronchiectasis and integrate multi-organ damage, and multi-modal data into routine patient evaluation. In this way, one can hope that we transition from an era of disease management to an era of personalised multi-faceted patient management.

REFERENCES

1. McLean KH. The histology of generalized pulmonary emphysema. I. The genesis of the early centrolobular lesion: focal emphysema. Australas Ann Med 1957;6(2):124–140.

2. Leopold JG, Gough J. The centrilobular form of hypertrophic emphysema and its relation to chronic bronchitis. Thorax 1957;12(3):219–235.

3. Heard BE. A pathological study of emphysema of the lungs with chronic bronchitis. Thorax 1958;13(2):136–149.

4. Wyatt JP, Fischer VW, Sweet HC. Panlobular emphysema: anatomy and pathodynamics. Dis Chest 1962;41(3):239–259.

5. Stern EJ, Frank MS. CT of the lung in patients with pulmonary emphysema: diagnosis, quantification, and correlation with pathologic and physiologic findings. *AJR Am J Roentgenol.* 1994;162:791–8.

6. Thurlbeck WM, Müller NL. Emphysema: definition, imaging, and quantification. *AJR Am J Roentgenol.* 1994;163:1017–25

7. Müller NL, Staples CA, Miller RR, Abboud RT. "Density mask". An objective method to quantitate emphysema using computed tomography. *Chest* 1988;94:782–787

8. Galbán CJ, Han MK, Boes JL, et al. Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression. *Nat Med.* 2012;18(11):1711–5.

9. Agnelli et al Angelini ED, Yang J, Balte PP, Hoffman EA, Manichaikul AW, Sun Y, Shen W, Austin JHM, Allen NB, Bleecker ER, Bowler R, Cho MH, Cooper CS, Couper D, Dransfield MT, Garcia CK, Han MK, Hansel NN, Hughes E, Jacobs DR, Kasela S, Kaufman JD, Kim JS, Lappalainen T, Lima J, Malinsky D, Martinez FJ, Oelsner EC, Ortega VE, Paine R, Post W, Pottinger TD, Prince MR, Rich SS, Silverman EK, Smith BM, Swift AJ, Watson KE, Woodruff PG, Laine AF, Barr RG. Pulmonary emphysema subtypes defined by unsupervised machine learning on CT scans. Thorax. 2023 Jun 2:thoraxjnl-2022-219158. doi: 10.1136/thorax-2022-219158.

10. Young AL, Bragman FJS, Rangelov B, Han MK, Galbán CJ, Lynch DA, Hawkes DJ, Alexander DC, Hurst JR; COPDGene Investigators. Disease Progression Modeling in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2020 Feb 1;201(3):294-302. doi: 10.1164/rccm.201908-1600OC.

11. https://www.gov.uk/government/news/new-lung-cancer-screening-roll-out-to-detect-cancer-sooner

12. Tisi S, Dickson JL, Horst C, Quaife SL, Hall H, Verghese P, Gyertson K, Bowyer V, Levermore C, Mullin AM, Teague J, Farrelly L, Nair A, Devaraj A, Hackshaw A, Hurst JR, Janes SM; SUMMIT Consortium. Detection of COPD in the SUMMIT Study Lung Cancer Screening Cohort using Symptoms and Spirometry. Eur Respir J. 2022 Jul 26:2200795. doi: 10.1183/13993003.00795-2022.

13. Goffin JR, Pond GR, Puksa S, Tremblay A, Johnston M, Goss G, Nicholas G, Martel S, Bhatia R, Liu G, Schmidt H, Atkar-Khattra S, McWilliams A, Tsao MS, Tammemagi MC, Lam S. Chronic obstructive pulmonary disease prevalence and prediction in a high-risk lung

cancer screening population. BMC Pulm Med. 2020 Nov 16;20(1):300. doi: 10.1186/s12890-020-01344-y

14. Xu F, Vasilescu DM, Kinose D, Tanabe N, Ng KW, Coxson HO, Cooper JD, Hackett TL, Verleden SE, Vanaudenaerde BM, Stevenson CS, Lenburg ME, Spira A, Tan WC, Sin DD, Ng RT, Hogg JC. The molecular and cellular mechanisms associated with the destruction of terminal bronchioles in COPD. Eur Respir J. 2022 May 26;59(5):2101411. doi: 10.1183/13993003.01411-2021.

15. Verleden SE, Kirby M, Everaerts S, Vanstapel A, McDonough JE, Verbeken EK, Braubach P, Boone MN, Aslam D, Verschakelen J, Ceulemans LJ, Neyrinck AP, Van Raemdonck DE, Vos R, Decramer M, Hackett TL, Hogg JC, Janssens W, Verleden GM, Vanaudenaerde BM. Small airway loss in the physiologically ageing lung: a cross-sectional study in unused donor lungs. Lancet Respir Med. 2021 Feb;9(2):167-174. doi: 10.1016/S2213-2600(20)30324-6.

16. Walsh CL, Tafforeau P, Wagner WL, Jafree DJ, Bellier A, Werlein C, Kühnel MP, Boller E, Walker-Samuel S, Robertus JL, Long DA, Jacob J, Marussi S, Brown E, Holroyd N, Jonigk DD, Ackermann M, Lee PD. Imaging intact human organs with local resolution of cellular structures using hierarchical phase-contrast tomography. Nat Methods. 2021 Dec;18(12):1532-1541. doi: 10.1038/s41592-021-01317-x.

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