Published in final edited form as:
J Thorac Imaging. 2013 September ; 28(5): 280–283. doi:10.1097/RTI.0b013e3182a0d805.

Establishing normal reference values in quantitative computed tomography of emphysema

Benjamin M. Smith, MD MS[1,2] and **R. Graham Barr, MD DrPH**[1,3]

[1]Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY

[2]Department of Medicine, McGill University Health Center, Montreal, Canada

[3]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY

Summary

Quantitative computed tomography (QCT) can provide reliable and valid measures of lung structure and volumes. Similar to lung function and volumes measured by spirometry, lung measures obtained by QCT vary by demographic and anthropomorphic factors including sex, race/ethnicity and height in asymptomatic non-smokers. Hence, some accounting for these factors is necessary to define abnormal from normal QCT values and disease severity. Similar to spirometry and cardiac volumes, prediction equations for QCT may be derived from a sample of asymptomatic individuals to estimate reference values.

This paper describes the methodology of reference equation development using, as an example, quantitative densitometry to detect pulmonary emphysema. The process described is generalizable to other QCT measures, including lung volumes, airway dimensions and gas-trapping. Pulmonary emphysema is defined morphologically by airspace enlargement with alveolar wall destruction and has been shown to correlate with low lung attenuation estimated by QCT. Deriving reference values for a normal quantity of low lung attenuation requires three steps: First, criteria that define normal must be established. Second, variables for inclusion must be selected based on an understanding of subject, scanner and protocol specific factors that influence lung attenuation. Finally, a reference sample of normal individuals must be selected that is representative of the population in which QCT will be used to detect pulmonary emphysema. Sources of bias and confounding inherent to reference values are also discussed.

Reference equation development is a multistep process that can define normal values for QCT measures such as lung attenuation. Normative reference values will increase the utility of QCT in both research and clinical practice.

Keywords

quantitative; computed tomography; emphysema; reference equation; prediction

Corresponding author: R. Graham Barr MD DrPH, Presbyterian Hospital Room 9E-105, 622 West 168th St, New York, NY 10032, rgb9@columbia.edu, Phone: 212-305-4895, Fax: 212-305-9349.

Introduction

Quantitative computed tomography (QCT) can provide reliable and valid measures of lung structure including parenchymal attenuation and airway dimensions.[1–9] These structural changes are important to the pathophysiology of many lung disorders, such as chronic obstructive pulmonary disease (COPD), emphysema, and asthma.[10,11] An understanding of the normal variation of QCT measures of lung structure is necessary in order to maximize its utility in research and clinical practice. The methodology of reference value derivation will be discussed here using, as an example, lung attenuation for detection of pulmonary emphysema. The concepts, however, can be extended to the development of reference values for other QCT measures, including lung and lobar volumes, airway dimensions and gas-trapping.

Pulmonary Emphysema and QCT

Pulmonary emphysema is defined morphologically as permanent enlargement of air spaces distal to the terminal bronchiole, accompanied by destruction of their walls.[12] Although emphysema is defined by gross and microscopic anatomic appearances, QCT has been shown to correlate well with pathologic specimens permitting detection *in vivo*, and can estimate the total and regional burden of emphysema.[1,13–18] In addition, QCT has superior reproducibility characteristics compared to visual assessment of emphysema.[3,9]

A widely used QCT measure of pulmonary emphysema is the percentage of lung voxels below a specific Hounsfield unit (HU) threshold (e.g., −910 HU or −950 HU).[5,19] First described by Müller and colleagues, percent emphysema is a continuous measure provides an estimate of the quantity of emphysema-like lung.[1] The term emphysema-like lung is emphasized because, despite significant statistical correlation with pathologic specimens,[1,15,16,18] percent emphysema can be influenced by several factors unrelated to emphysema and can be observed among individuals without emphysema assessed visually.[5,20,21]

Variation in Lung Volumes and Percent Emphysema in Healthy Individuals

Lung function and volumes measured by spirometry and plethysmography have long been noted to vary substantially in apparently healthy individuals by demographic factors and body size.[22–30] Hankinson reference equations, which allow calculation of a predicted normal value and limit of normal for an individual of a given age, sex, race/ethnicity and height, are used widely in clinical and research settings to account for this variation.[27] Recently statements recommend that airflow limitation, for example, be defined as a value below the lower limit of normal based upon such equations.[31] A similar approach has been adopted for cardiac volumes.[32,33]

Total lung volume and other thoracic volumes measured on QCT are highly likely to exhibit similar variation by demographic factors and body size in asymptomatic individuals, as are ratios such as the ratio of low lung attenuation to total lung volume, a metric of emphysema severity.[1] Multiple studies confirm this supposition and demonstrate that percent emphysema varies in asymptomatic individuals by, at a minimum, age, sex and body size.[2,20,34–39] This variation in asymptomatic individuals is often large and, not infrequently, larger than that observed in individuals with disease. Hence, in defining normal values for percent emphysema from abnormal, it may be helpful to account for these factors and possibly others in order to permit accurate classification of emphysema status and severity using QCT.

Approaches to Defining Disease

The optimal approach to defining a threshold of abnormality for diseases that are common in the general population is not obvious and varies considerably by disease. Arguably, the best approach to define such a disease, particularly an asymptomatic disease, is to pick a threshold above or below which treatment is proven to improve outcomes. Hypertension is an example of a disease defined following this approach. Randomized clinical trials have demonstrated a proven benefit (i.e., reduced cardiovascular events) of reducing systolic and diastolic blood pressure to 140 and 90 mm Hg,[40–43] respectively. Subsequent randomized clinical trials that targeted blood pressure reduction below these thresholds failed to show a benefit for clinical events,[44,45] hence hypertension is defined for most patients by these criteria.[46] Similarly, diabetes is defined by an absolute glycemic threshold at which specific complications (e.g., diabetic retinopathy) occur.[47] In the context of emphysema, a symptomatic disease for which effective, specific therapies are lacking,[48] a reasonable approach may be to define normal based on the distribution of the measure in asymptomatic individuals in the general population. This strategy has the goal of helping to define the relevance of QCT measures of emphysema to clinical practice and to facilitate the study of the pathobiology of emphysema and development of novel, emphysema-specific therapies.

Establishing Normal Reference Values for Percent Emphysema

Percent emphysema is a continuous measure that correlates with pathologic emphysema but also varies in healthy individuals. [1,15,16,18,20,21,36,37] Similar to spirometry,[27] development of reference equations for percent emphysema should attempt to minimize misclassification of disease (i.e., emphysema) by accounting for normal variation from subject and scanner factors. Once these factors have been measured in a representative sample of healthy individuals, regression modeling can be used to derive reference equations that minimize differences between predicted and observed values (i.e., residuals). Knowing the residual variance, disease presence or severity may then be defined in a study or clinical population based on observed deviation from normal reference values.[27,30,49] The process of reference equation development will be discussed in detail below.

Defining who is normal

Defining normal is not trivial. In the context of a QCT measure to detect pulmonary emphysema, the ideal definition of normal is anyone who is disease-free, i.e., without emphysema. In the absence of a gold-standard method of detecting emphysema pre-mortem, one might reasonably begin by excluding individuals with respiratory symptoms or diagnoses of chronic lower respiratory disease. Indeed, this approach has been used to develop reference equations for spirometry.[27,30] It should be noted that defining normal by the absence of respiratory symptoms or disease may introduce some misclassification by including individuals with emphysema who underreport symptoms or do not seek medical attention.[50] Similarly, respiratory diseases other than emphysema that influence lung attenuation may also be excluded from the reference sample. For example, gas-trapping is a physiologic consequence of airways obstruction that is associated with low lung attenuation that occurs in asthma.[2] Excluding individuals with asthma-related respiratory symptoms and gas-trapping may bias the derived lung attenuation reference values for detection of emphysema. This inherent limitation to defining normal must be kept in mind when using reference values to define disease.[51]

Knowledge of disease risk factors can also help define normal individuals. For example, smoking is the major risk factor for COPD and low lung function; hence reference equations used to define normal values for spirometry exclude individuals with any history of smoking.[27,30] Smoking is also a risk factor for centrilobular emphysema,[52] although the

relationship between smoking history (i.e., pack-years) and percent emphysema is much weaker than that for lung function.[53] Nonetheless, exclusion of smokers may help to minimize misclassification in the reference sample.

However, current smoking appears to paradoxically influence lung attenuation independent of emphysema, possibly related to increased inflammatory cells in the lung of current smokers compared to former smokers.[38] Therefore, excluding current smokers completely will mean that the derived reference values for emphysema will be biased, potentially severely, when applied to current smokers. An alternative approach may be to include a secondary analysis in which current smokers are included in order to allow estimation of a term in the regression model that accounts for the difference in lung attenuation associated with current smoking or cigarettes per day.

Selecting predictors of variation in percent emphysema

Optimal use of reference values to detect emphysema by QCT requires that other sources of lung attenuation variation are known. Elsewhere in this issue of the *Journal of Thoracic Imaging* Coxson has reviewed sources of variation in QCT of the lungs. Briefly, with respect to lung attenuation these can be divided into scanner, protocol and subject-specific factors. Scanner-specific factors include model and manufacturer (particularly for newer scanners) whereas protocol-specific factors include tube current, slice thickness and number, reconstruction algorithm, and attenuation threshold. Provided a large enough reference sample with accurate ascertainment of these variables, a derived reference equation will account for much of the variability introduced by these factors. Scanner and protocol factors in the reference sample used to derive reference equations should be representative of those in the population where QCT will be applied. Although protocol-specific factors can be fixed by a highly standardized protocol, as used in most contemporary studies, scanner changes usually necessitate protocol changes. Scanner changes therefore represent a particular for challenge for reference equation development given the heterogeneity and rapid evolution of CT technology.(Ref Newell CT protocols from this issue)

Subject-specific factors known to influence lung attenuation include age, gender, body size, socio-economic status, depth of inspiration, smoking, and gas-trapping.[2,20,34–39] Based on population-based studies of spirometry, one might speculate that QCT measures of lung structure also differ by race-ethnicity.[27,30,54] Inclusion of these variables in a regression model can, if necessary, account for differences in lung attenuation associated with these factors. It should be noted, however, that these predictors may directly or indirectly mask true causes (and presence) of emphysema. For example, low body weight may be causally related to emphysema.[55] Inclusion of a body weight term in reference equations would obscure this relationship. Furthermore, differences in lung attenuation associated with subject specific factors may reflect confounding by an unmeasured variable that causes emphysema. For example, exposure to biomass fuel combustion in developing countries may cause emphysema to differ by gender. If this exposure is not included in the reference regression model, the role of biomass fuel combustion would be masked by gender. Users of reference equations should be aware of the inputs used as predictors and the potential for over adjustment and residual confounding.[51]

Selecting a representative sample

The sample of asymptomatic individuals used to derive percent emphysema reference equations should be representative of the population in which QCT will be applied to detect emphysema. Specifically, the sample should reflect the range of scanner and subject variables encountered in the general population from which cases of disease (i.e., COPD or emphysema) are to be defined. Furthermore, the characteristics of the reference sample,

including scanner and subject specific factors, should be reported. This will help to limit extrapolation of reference values beyond the observed data in the derivation sample. Finally, a large and diverse reference sample is essential in order to increase the precision of normal estimates by accounting for the numerous permutations of input predictors.

Summary

QCT can provide reliable and valid measures of lung structure *in vivo*. Application of this technology to study the biology and clinical significance of lung disease will be facilitated by normal reference values. Derivation of reference equations is a multistep process. First, one must define a normal sample population (i.e., free of the disease of interest). Second, one must identify scanner and subject specific factors that influence QCT measures independent of the disease of interest. Third, regression of QCT measures must be performed on a large reference sample representative of the population in which these measures will be applied. Developers and users of reference equations should have an understanding of the bias and confounding inherent in using normal reference values. Analogous to reference values for spirometry, establishing reference values for QCT will reduce misclassification of emphysema and help advance research and clinical management of lung disease.

Acknowledgments

Conflicts of interest and sources of funding: Preparation of this manuscript was supported by National Institutes of Health grants for the MESA COPD and MESA Lung Studies (HL083091 and HL077612), and the Quebec Health Research Fund. RGB holds grants from National Institutes of Health (NIH), US Environmental Protection Agency and Alpha-1 Foundation. BMS is funded by the Quebec health research fund.

REFERENCES

1. Müller NL, Staples CA, Miller RR, Abboud RT. "Density mask". An objective method to quantitate emphysema using computed tomography. Chest. 1988; 94:782–787. [PubMed: 3168574]
2. Newman KB, Lynch DA, Newman LS, Ellegood D, Newell JD Jr. Quantitative computed tomography detects air trapping due to asthma. Chest. 1994; 106:105–109. [PubMed: 8020254]
3. Bankier AA, De Maertelaer V, Keyzer C, Gevenois PA. Pulmonary emphysema: subjective visual grading versus objective quantification with macroscopic morphometry and thin-section CT densitometry. Radiology. 1999; 211:851–858. [PubMed: 10352615]
4. Nakano Y, Muro S, Sakai H, et al. Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. Am J Respir Crit Care Med. 2000; 162:1102–1108. [PubMed: 10988137]
5. Madani A, Keyzer C, Gevenois PA. Quantitative computed tomography assessment of lung structure and function in pulmonary emphysema. Eur Respir J. 2001; 18:720–730. [PubMed: 11716178]
6. Nakano Y, Wong JC, de Jong PA, et al. The prediction of small airway dimensions using computed tomography. Am J Respir Crit Care Med. 2005; 171:142–146. [PubMed: 15516531]
7. Hasegawa M, Nasuhara Y, Onodera Y, et al. Airflow limitation and airway dimensions in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2006; 173:1309–1315. [PubMed: 16556695]
8. Aysola RS, Hoffman EA, Gierada D, et al. Airway remodeling measured by multidetector CT is increased in severe asthma and correlates with pathology. Chest. 2008; 134:1183–1191. [PubMed: 18641116]
9. Cavigli E, Camiciottoli G, Diciotti S, et al. Whole-lung densitometry versus visual assessment of emphysema. Eur Radiol. 2009; 19:1686–1692. [PubMed: 19224221]
10. Hogg JC. Pathology of asthma. J Allergy Clin Immunol. 1993; 92:1–5. [PubMed: 8335845]

11. McDonough JE, Yuan R, Suzuki M, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. N Engl J Med. 2011; 365:1567–1575. [PubMed: 22029978]
12. The definition of emphysema. Report of a National Heart, Lung, and Blood Institute, Division of Lung Diseases workshop. Am Rev Respir Dis. 1985; 132:182–185. [PubMed: 4014865]
13. Hayhurst MD, MacNee W, Flenley DC, et al. Diagnosis of pulmonary emphysema by computerised tomography. Lancet. 1984; 2:320–322. [PubMed: 6146866]
14. Gould GA, Macnee W, Mclean A, et al. Ct Measurements of Lung Density in Life Can Quantitate Distal Airspace Enlargement - an Essential Defining Feature of Human Emphysema. Am Rev Respir Dis. 1988; 137:380–392. [PubMed: 3341629]
15. Gevenois PA, de Maertelaer V, De Vuyst P, Zanen J, Yernault JC. Comparison of computed density and macroscopic morphometry in pulmonary emphysema. Am J Respir Crit Care Med. 1995; 152:653–657. [PubMed: 7633722]
16. Gevenois PA, DeVuyst P, deMaertelaer V, et al. Comparison of computed density and microscopic morphometry in pulmonary emphysema. Am J Resp Crit Care. 1996; 154:187–192.
17. Coxson HO, Rogers RM, Whittall KP, et al. A quantification of the lung surface area in emphysema using computed tomography. Am J Respir Crit Care Med. 1999; 159:851–856. [PubMed: 10051262]
18. Madani A, Zanen J, de Maertelaer V, Gevenois PA. Pulmonary emphysema: Objective quantification at mufti-detector row CT - Comparison with macroscopic and microscopic morphometry. Radiology. 2006; 238:1036–1043. [PubMed: 16424242]
19. Lynch DA, Newell JD. Quantitative Imaging of COPD. J Thorac Imag. 2009; 24:189–194.
20. Madani A, Van Muylem A, Gevenois PA. Pulmonary emphysema: effect of lung volume on objective quantification at thin-section CT. Radiology. 2010; 257:260–268. [PubMed: 20663967]
21. Mets OM, van Hulst RA, Jacobs C, van Ginneken B, de Jong PA. Normal range of emphysema and air trapping on CT in young men. AJR Am J Roentgenol. 2012; 199:336–340. [PubMed: 22826394]
22. Hutchinson J. On the capacity of the lungs, and on the respiratory functions, with a view of establishing a precise and easy method of detecting disease by the spirometer. Medico-chirurgical transactions. 1846; 29:137–252.
23. Goldman HI, Becklake MR. Respiratory function tests; normal values at median altitudes and the prediction of normal results. Am Rev Tuberc. 1959; 79:457–467. [PubMed: 13650117]
24. Crapo RO, Morris AH, Clayton PD, Nixon CR. Lung volumes in healthy nonsmoking adults. Bull Eur Physiopathol Respir. 1982; 18:419–425. [PubMed: 7074238]
25. Jacobs DR Jr, Nelson ET, Dontas AS, Keller J, Slattery ML, Higgins M. Are race and sex differences in lung function explained by frame size? The CARDIA Study. Am Rev Respir Dis. 1992; 146:644–649. [PubMed: 1519841]
26. Burchfiel CM, Marcus EB, Sharp DS, et al. Characteristics associated with rapid decline in forced expiratory volume. Ann Epidemiol. 1996; 6:217–227. [PubMed: 8827157]
27. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999; 159:179–187. [PubMed: 9872837]
28. Harik-Khan RI, Fleg JL, Muller DC, Wise RA. The effect of anthropometric and socioeconomic factors on the racial difference in lung function. Am J Respir Crit Care Med. 2001; 164:1647–1654. [PubMed: 11719304]
29. Kiefer EM, Hankinson JL, Barr RG. Similar relation of age and height to lung function among Whites, African Americans, and Hispanics. Am J Epidemiol. 2011; 173:376–387. [PubMed: 21242304]
30. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. European Respiratory Journal. 2012; 40:1324–1343. [PubMed: 22743675]
31. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005; 26:948–968. [PubMed: 16264058]
32. Natori S, Lai S, Finn JP, et al. Cardiovascular function in multi-ethnic study of atherosclerosis: normal values by age, sex, and ethnicity. AJR Am J Roentgenol. 2006; 186:S357–S365. [PubMed: 16714609]

33. Kawut SM, Lima JA, Barr RG, et al. Sex and race differences in right ventricular structure and function: the multi-ethnic study of atherosclerosis-right ventricle study. Circulation. 2011; 123:2542–2551. [PubMed: 21646505]
34. Soejima K, Yamaguchi K, Kohda E, et al. Longitudinal follow-up study of smoking-induced lung density changes by high-resolution computed tomography. Am J Resp Crit Care. 2000; 161:1264–1273.
35. Camp PG, Coxson HO, Levy RD, et al. Sex Differences in Emphysema and Airway Disease in Smokers. Chest. 2009; 136:1480–1488. [PubMed: 19617404]
36. Irion KL, Marchiori E, Hochhegger B, et al. CT quantification of emphysema in young subjects with no recognizable chest disease. AJR Am J Roentgenol. 2009; 192:W90–W96. [PubMed: 19234245]
37. Zach JA, Newell JD Jr, Schroeder J, et al. Quantitative Computed Tomography of the Lungs and Airways in Healthy Nonsmoking Adults. Invest Radiol. 2012
38. Ashraf H, Lo P, Shaker SB, et al. Short-term effect of changes in smoking behaviour on emphysema quantification by CT. Thorax. 2011; 66:55–60. [PubMed: 20978026]
39. Lovasi GS, Diez Roux AV, Hoffman EA, et al. Socioeconomic status is positively associated with percent emphysema on CT scan: The MESA lung study. Acad Radiol. 2011; 18:199–204. [PubMed: 21232685]
40. Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet. 1990; 335:827–838. [PubMed: 1969567]
41. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA. 1991; 265:3255–3264. [PubMed: 2046107]
42. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet. 1997; 350:757–764. [PubMed: 9297994]
43. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998; 351:1755–1762. [PubMed: 9635947]
44. Arguedas JA, Perez MI, Wright JM. Treatment blood pressure targets for hypertension. Cochrane Database Syst Rev. 2009:CD004349. [PubMed: 19588353]
45. Group AS, Cushman WC, Evans GW, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010; 362:1575–1585. [PubMed: 20228401]
46. Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003; 42:1206–1252. [PubMed: 14656957]
47. Inzucchi S, Bergenstal R, Fonseca V, et al. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2010; 33:S62–S69. [PubMed: 20042775]
48. Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med. 2003; 348:2059–2073. [PubMed: 12759479]
49. Global Initiative for Chronic Obstructive Lung Disease strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: an Asia-Pacific perspective. Respirology. 2005; 10:9–17. [PubMed: 15691232]
50. Stanojevic S, Wade A, Stocks J. Reference values for lung function: past, present and future. Eur Respir J. 2010; 36:12–19. [PubMed: 20595163]
51. Marks GB. Are reference equations for spirometry an appropriate criterion for diagnosing disease and predicting prognosis? Thorax. 2012; 67:85–87. [PubMed: 21825082]
52. Anderson AE Jr, Hernandez JA, Holmes WL, Foraker AG. Pulmonary emphysema. Prevalence, severity, and anatomical patterns in macrosections, with respect to smoking habits. Archives of Environmental Health. 1966; 12:569–577. [PubMed: 5930647]

53. Powell R, Davidson D, Divers J, et al. Genetic ancestry and the relationship of cigarette smoking to lung function and per cent emphysema in four race/ethnic groups: a cross-sectional study. Thorax. 2013

54. Hankinson JL, Kawut SM, Shahar E, Smith LJ, Stukovsky KH, Barr RG. Performance of American Thoracic Society-recommended spirometry reference values in a multiethnic sample of adults: the multi-ethnic study of atherosclerosis (MESA) lung study. Chest. 2010; 137:138–145. [PubMed: 19741060]

55. Coxson HO, Chan IH, Mayo JR, Hlynsky J, Nakano Y, Birmingham CL. Early emphysema in patients with anorexia nervosa. Am J Respir Crit Care Med. 2004; 170:748–752. [PubMed: 15256394]