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The Role of Imaging in the Assessment of Severe Asthma

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Abstract

Purpose of Review—This review aims to summarize the most recent evidence related to imaging and severe asthma, both with regard to advances in imaging research and to their current and potential clinical implications.

Recent Findings—Recent work in imaging in severe asthma has principally been using computed tomography (CT) and magnetic resonance imaging (MRI), as well as the integration of the two. Some of the most notable findings include the use of CT imaging biomarkers to create unique clusters of asthmatics, and the use of co-registration to link CT images of airways with regional variation in ventilation in MRI. In addition, temporal studies have shown that some the ventilation defects found using MRI in asthmatics are intermittent and others are persistent, but both are associated with lower lung function.

Summary—The role of imaging in severe asthma currently is primarily in the exclusion of comorbid or other conditions, or in the assessment for complications in the setting of acute decompensation. A rapidly expanding body of literature using CT and MRI suggests that these tools may soon be of utility in the chronic management of the disease.

Keywords

asthma; imaging; computed tomography; magnetic resonance imaging

Introduction

Asthma comprises a broad range of patient phenotypes, classically characterized by recurrent episodes of airway obstruction and reversible airflow limitation, usually in the setting of chronic airway inflammation and bronchial hyper-responsiveness.[1, 2] The term “severe asthma” does not relate to a specific pathobiological entity or even a specific phenotype, but rather occurs in those patients who are unable to maintain control of their

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Conflicts of Interest

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disease, never attain control of their disease, or who require treatment with high dose inhaled or systemic corticosteroids as well as a second controller medication.[1, 3] Although this group represents only 5–10% of asthmatics as a whole, they account for nearly 50% of the healthcare costs related to asthma, thus any strategies that can improve the diagnosis and management of these patients may have a significant impact both on their quality of life and on the economic burden of the disease.[1] Over the past several decades many investigators have shown that multiple imaging modalities can be used to reliably differentiate those with severe asthma from those with milder disease, and increasingly there is discussion of what role imaging may play in both diagnosing and monitoring severe asthmatics. As there have been multiple prior reviews of this literature, in this review, we briefly discuss both older, but important, imaging studies of asthmatics, and place particular emphasis on recent advances in the imaging of severe asthmatics.[4–8]

Chest Radiography

The role of chest radiography in chronic management of asthma has been discussed multiple times elsewhere and there have been few recent advances in this area.[7] However, it is worth noting that chest radiography continues to play an important role in the management of patients with severe asthma in the acute setting, such as during an admission for asthma exacerbation. In a small study of 58 patients admitted for asthma exacerbations, White et al, reported major radiograph abnormalities in 34% and minor abnormalities in an additional 41%.[9] Of these findings, pneumothorax and pneumomediastinum are by far the most concerning. The rate of pneumothorax in patients admitted for status asthmaticus has been reported as somewhere between 0.5 and 2.5%, but in at least one series, it was the immediate cause of death in 27% of those who died from their asthma exacerbation.[10, 11] While there is some debate about the sensitivity of chest radiography for pneumothoraces, it remains a highly effective screening tool for large pneumothoraces, and when performed in the left lateral decubitus position, is up to 88% sensitive for pneumothorax under experimental conditions.[12]

Computed Tomography

Clinically, the role of computed tomography (CT) imaging in asthma is primarily related to the diagnosis of complications and associated conditions. As mentioned above, pneumothorax is a rare but severe complication of severe asthma, which primarily occurs in the setting of status asthmaticus.[10, 11] Chest CT is generally considered the gold standard for diagnosing pneumothorax and is especially useful in severe asthmatics with an acute decompensation, or whenever the clinical setting suggests the possibility of a pneumothorax, such as in the setting of high airway pressures on mechanical ventilation.[10, 13, 14] CT scanning may also be useful for diagnosing diseases associated with asthma, such as allergic bronchopulmonary aspergillosis, eosinophilic pneumonia, and eosinophilic granulomatosis with polyangiitis.[7]

Much of the work on the CT radiographic correlates of pathologic findings in severe asthma was detailed in the excellent review on the subject in this journal by Walker et al in 2012. Qualitative studies of CT scans performed on severe asthmatics have shown relatively high

rates of bronchiectasis and bronchial wall thickening.[6, 15] These findings have been associated with worse lung function and longer disease duration, but these associations have not been uniform across studies, and whether these findings reflect an underlying pathobiological cause of disease severity or whether they are simply natural manifestations of disease progression is unclear.[6, 15–22]

More recently, there has been a growing focus on quantitative CT measures of disease severity in asthma. Similar to the qualitative assessment of chest radiographs, the main findings of interest on CT scans of asthmatics, especially severe asthmatics, can be broken down into those that relate to morphologic changes in the larger airways, and those that suggest small airway dysfunction, manifested primarily as regional variation of hyperinflation. With regard to the quantitative analysis of the larger airways in particular, much of the work has focused on CT measurements of the airway wall thickness, wall area and lumen area. For instance, Aysola et al performed automated measurements of third generation airways in 123 subjects as part of the National Institutes of Health Severe Asthma Research Program. They found that while airway wall thickness was not higher in severe asthmatics when compared to those with mild asthma or no disease, wall thickness percentage (wall thickness divided by outer airway diameter) was higher in those with severe asthma. Wall thickness percentage was also inversely correlated with baseline percent predicted forced expiratory volume in one second (FEV1%) and positively correlated with change in FEV1% with bronchodilator challenge. They found similar results for the airway wall area percentage (airway wall area divided by the total area of the airway), and for the airway lumen area percentage (airway lumen area divided by the total area of the airway). [23] In a subgroup of subjects who underwent endobronchial biopsies, Aysola et al found that the wall area percentage also correlated with the ratio of epithelium to lamina reticularis area, suggesting that the findings on CT represented radiographic evidence of airway remodeling (Figure 1).[23] Others, including Hartley et al, have recently shown that in asthmatics wall area percentage in particular is one of the strongest predictors of lung function impairment.[24] Another interesting quantitative CT measure, described by Brillet et al in a small series of patients with severe asthma, is focal airway stenoses measured as a greater than 50% decrease of the lumen area. The authors found that severe asthmatics had more focal bronchial stenoses than those without asthma and suggested that this may be the result of airways remodeling and increased basal tone.[25] Further studies might shed light on the clinical potential of this measure.

It should be noted that, as pointed out by Walker et al, findings related to clinical associations with CT based airway measurements in asthma have not been uniform across the literature and may be subject to inter-center variability in patient population and imaging analysis protocols.[6, 26, 27] In fact, it is not clear even which, if any, generation of airway best demonstrates these changes. For example, Thomson et al found an association between the airway lumen area of fifth generation airways and poor symptom control among smokers with asthma, but they did not find any such relationship with third generation airways, nor was it evident in a study of nonsmoking asthmatics by Kaminska et al.[28, 29] Finally, the density of the airway wall itself has also been shown by Lederlin et al to be higher in asthmatics than in normal controls, and may be more strongly correlated with lung function than the aforementioned geometric airway measures.[30]

While the size of the small airways places them below the level of resolution of CT scanning, the results of asthma's effect on these airways can be visualized as air trapping. Air trapping can be objectively measured as changes in density on CT.[6, 31, 32] This can be quantified in a variety of ways, but is most commonly reported in absolute terms on either inspiratory or expiratory CT scans as the volume of tissue with a density below a certain Hounsfield unit cutoff or as the ratio or difference between the mean lung density on expiratory CT scan and inspiratory CT scan.[6, 33–36] For instance, Gupta et al showed that patients with severe asthma have greater air trapping measured as an expiratory to inspiratory density ratio than those with mild disease and those without asthma.[36] Interestingly, by combining these density measures with the geometric airway measures discussed above, as well as with a measure of the complexity of the tracheobronchial tree, Gupta et al were able to identify three novel asthma phenotypes with distinct clinical and radiographic features.[36] The use of these techniques to begin to identify unique patient groups suggests that CT imaging may be useful for identifying those individuals who may benefit from certain therapies in the future, especially as others have begun to evaluate the role of CT imaging in monitoring response to therapy.[37]

Finally, while whole lung measures of air trapping are useful, asthma is often characterized by regional variations in ventilation due to small airways disease. Through the use of xenon enhanced CT this regional variation can be assessed more directly than with standard CT imaging, but until recently this technique was limited by technical issues relating to the changes in lung volume between scans.[38, 39] The development of dual energy xenon enhanced CT imaging has overcome that problem.[38, 40] In their report on their initial experience with this technique Chae et al showed that a ventilation defect score in stable asthmatics correlated with residual lung volume and with the FEV1 to forced vital capacity (FVC) ratio.[40] Kim et al demonstrated that this score was different between asthmatics and normal controls both at baseline and after methacholine challenge.[38] Further research is needed to best determine the role of this imaging technique in the assessment of asthmatics and in severe asthmatics in particular.

Magnetic Resonance Imaging

While primarily limited to the research setting, magnetic resonance imaging (MRI) has been demonstrated to have several potential advantages for the imaging of patients with severe asthma. Chief among those is its ability to provide images that depict the regional distribution of ventilation defects in asthma across the entire lung.[8] This is particularly true of MRI that utilizes hyperpolarized gas, typically either hyperpolarized helium (^3He) or xenon (^{129}Xe). Quantified measures of these ventilation defects have been shown to be associated with lower FEV1/FVC ratio, and higher methacholine responsiveness and expired nitric oxide levels in adults as well as with higher inhaled corticosteroid dose, and lower FEV1/FVC ratio and Asthma Control Test scores in children.[41, 42] The primary clinical limitation of this technique, especially in those with severe disease, is that the inhaled gas, which in the case of the more commonly utilized ^3He method is a helium-nitrogen mixture, is anoxic and displaces air from the lungs. This results in desaturations during the breath hold maneuver, though typically not less than 90%.[8, 43] Ongoing work on oxygen enhanced MRI imaging may ameliorate that problem.[44] An additional concern is that the

breath hold maneuver is often long, up to 20 seconds, which may not be feasible for patients with more severe asthma.

There are several other limitations to the use of hyperpolarized MRI imaging in particular, including the need for specialized gas mixtures that are only approved for investigational use, and the inability to clearly identify anatomic structures.[8, 45] This had led to the use of co-registration of hyperpolarized MRI images with standard MRI images or with CT images as well as investigation into the use of other approaches to standard MRI imaging which may be able to provide similar information.[42, 45–47] This work has led to several fascinating findings, including the association between MRI measured ventilation defects and CT measurements of airway remodeling as well as the presence of both intermittent and persistent ventilation defects in patients with asthma.[42, 48] Interestingly the percent of the lung comprised of both the intermittent ventilation defects and persistent defects is inversely associated with FEV1/FVC ratio (Figure 2).[48] In addition to improving our overall understanding of the disease, the ability of MRI to measure regional variation in ventilation may be particularly useful for severe asthmatics for whom bronchial thermoplasty is considered.[49] For instance, in a small study Thomen et al quantified lung ventilation in bronchopulmonary segments in severe asthmatics. They found that compared to controls, those with severe asthma have 2.3 times higher median ventilation defect percentage and that ventilation defects decrease over time after bronchial thermoplasty.[49] These findings suggest that imaging might be helpful to guide and quantify response to therapy.

Conclusion

Multiple imaging modalities including chest radiography, CT, and MRI have been shown to be useful in the evaluation of patients with severe asthma. Clinically, these approaches are most commonly used for the evaluation for complications such as pneumothoraces, but many of the more research focused techniques, especially quantitative measures of airway morphology, may soon find their way into larger clinical practice as experience with them grows and the ability to perform automated measurements improves. Further work evaluating such clinical use, as well as multi-center studies investigating the role of using these measures longitudinally to monitor disease progression and response to therapy is needed.

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References

1. Ray A, Raundhal M, Oriss TB, et al. Current concepts of severe asthma. *J Clin Invest*. 2016; 126:2394–403. [PubMed: 27367183]
2. Martinez FD, Vercelli D. Asthma. *Lancet*. 2013; 382:1360–72. [PubMed: 24041942]
3. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *The European respiratory journal*. 2014; 43:343–73. [PubMed: 24337046]

4. Tashkin DP, de Lange EE. Imaging of the distal airways. *The Journal of allergy and clinical immunology*. 2009; 124:S78–83. [PubMed: 19962040]
5. Walker C, Gupta S, Raj V, et al. Imaging advances in asthma. *Expert Opin Med Diagn*. 2011; 5:453–65. [PubMed: 23484630]
6. Walker C, Gupta S, Hartley R, Brightling CE. Computed tomography scans in severe asthma: utility and clinical implications. *Current opinion in pulmonary medicine*. 2012; 18:42–7. [PubMed: 22112997]
7. Richards JC, Lynch D, Koelsch T, Dyer D. Imaging of Asthma. *Immunol Allergy Clin North Am*. 2016; 36:529–45. [PubMed: 27401624]
8. Castro M, Fain SB, Hoffman EA, et al. Lung imaging in asthmatic patients: the picture is clearer. *The Journal of allergy and clinical immunology*. 2011; 128:467–78. [PubMed: 21636118]
9. White CS, Cole RP, Lubetsky HW, Austin JH. Acute asthma. Admission chest radiography in hospitalized adult patients. *Chest*. 1991; 100:14–6. [PubMed: 2060333]
10. Afessa B, Morales I, Cury JD. Clinical course and outcome of patients admitted to an ICU for status asthmaticus. *Chest*. 2001; 120:1616–21. [PubMed: 11713143]
11. Scoggin CH, Sahn SA, Petty TL. Status asthmaticus. A nine-year experience. *Jama*. 1977; 238:1158–62. [PubMed: 578161]
12. Carr JJ, Reed JC, Choplin RH, et al. Plain and computed radiography for detecting experimentally induced pneumothorax in cadavers: implications for detection in patients. *Radiology*. 1992; 183:193–9. [PubMed: 1549671]
13. Paganin F, Trussard V, Seneterre E, et al. Chest radiography and high resolution computed tomography of the lungs in asthma. *The American review of respiratory disease*. 1992; 146:1084–7. [PubMed: 1416399]
14. Porpodis K, Zarogoulidis P, Spyrtos D, et al. Pneumothorax and asthma. *Journal of thoracic disease*. 2014; 6(Suppl 1):S152–61. [PubMed: 24672689]
15. Gupta S, Siddiqui S, Halder P, et al. Qualitative analysis of high-resolution CT scans in severe asthma. *Chest*. 2009; 136:1521–8. [PubMed: 19542254]
16. Siddiqui S, Gupta S, Cruse G, et al. Airway wall geometry in asthma and nonasthmatic eosinophilic bronchitis. *Allergy*. 2009; 64:951–8. [PubMed: 19210350]
17. Paganin F, Seneterre E, Chanez P, et al. Computed tomography of the lungs in asthma: influence of disease severity and etiology. *American journal of respiratory and critical care medicine*. 1996; 153:110–4. [PubMed: 8542102]
18. Grenier P, Mourey-Gerosa I, Benali K, et al. Abnormalities of the airways and lung parenchyma in asthmatics: CT observations in 50 patients and inter- and intraobserver variability. *Eur Radiol*. 1996; 6:199–206. [PubMed: 8797980]
19. Yilmaz S, Ekici A, Ekici M, Keles H. High-resolution computed tomography findings in elderly patients with asthma. *Eur J Radiol*. 2006; 59:238–43. [PubMed: 16621393]
20. Takemura M, Niimi A, Minakuchi M, et al. Bronchial dilatation in asthma: relation to clinical and sputum indices. *Chest*. 2004; 125:1352–8. [PubMed: 15078745]
21. Lynch DA, Newell JD, Tschomper BA, et al. Uncomplicated asthma in adults: comparison of CT appearance of the lungs in asthmatic and healthy subjects. *Radiology*. 1993; 188:829–33. [PubMed: 8351357]
22. Bumbacea D, Campbell D, Nguyen L, et al. Parameters associated with persistent airflow obstruction in chronic severe asthma. *The European respiratory journal*. 2004; 24:122–8. [PubMed: 15293614]
23. 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; 134:1183–91. [PubMed: 18641116]
24. Hartley RA, Barker BL, Newby C, et al. Relationship between lung function and quantitative computed tomographic parameters of airway remodeling, air trapping, and emphysema in patients with asthma and chronic obstructive pulmonary disease: A single-center study. *The Journal of allergy and clinical immunology*. 2016; 137:1413–22. e12. [PubMed: 27006248]

25. Brillet PY, Debray MP, Golmard JL, et al. Computed tomography assessment of airways throughout bronchial tree demonstrates airway narrowing in severe asthma. *Academic radiology*. 2015; 22:734–42. [PubMed: 25882092]
26. Niimi A, Matsumoto H, Amitani R, et al. Airway wall thickness in asthma assessed by computed tomography. Relation to clinical indices. *American journal of respiratory and critical care medicine*. 2000; 162:1518–23. [PubMed: 11029371]
27. Gupta S, Siddiqui S, Haldar P, et al. Quantitative analysis of high-resolution computed tomography scans in severe asthma subphenotypes. *Thorax*. 2010; 65:775–81. [PubMed: 20805170]
28. Kaminska M, Foley S, Maghni K, et al. Airway remodeling in subjects with severe asthma with or without chronic persistent airflow obstruction. *The Journal of allergy and clinical immunology*. 2009; 124:45–51. e1–4. [PubMed: 19481790]
29. Thomson NC, Chaudhuri R, Spears M, et al. Poor symptom control is associated with reduced CT scan segmental airway lumen area in smokers with asthma. *Chest*. 2015; 147:735–44. [PubMed: 25356950]
30. Lederlin M, Laurent F, Portron Y, et al. CT attenuation of the bronchial wall in patients with asthma: comparison with geometric parameters and correlation with function and histologic characteristics. *AJR American journal of roentgenology*. 2012; 199:1226–33. [PubMed: 23169712]
31. Guckel C, Wells AU, Taylor DA, et al. Mechanism of mosaic attenuation of the lungs on computed tomography in induced bronchospasm. *Journal of applied physiology*. 1999; 86:701–8. [PubMed: 9931211]
32. Muller NL, Staples CA, Miller RR, Abboud RT. “Density mask”. An objective method to quantitate emphysema using computed tomography. *Chest*. 1988; 94:782–7. [PubMed: 3168574]
33. Busacker A, Newell JD Jr, Keefe T, et al. A multivariate analysis of risk factors for the air-trapping asthmatic phenotype as measured by quantitative CT analysis. *Chest*. 2009; 135:48–56. [PubMed: 18689585]
34. Gono H, Fujimoto K, Kawakami S, Kubo K. Evaluation of airway wall thickness and air trapping by HRCT in asymptomatic asthma. *The European respiratory journal*. 2003; 22:965–71. [PubMed: 14680087]
35. Newman KB, Lynch DA, Newman LS, et al. Quantitative computed tomography detects air trapping due to asthma. *Chest*. 1994; 106:105–9. [PubMed: 8020254]
36. Gupta S, Hartley R, Khan UT, et al. Quantitative computed tomography-derived clusters: Redefining airway remodeling in asthmatic patients. *The Journal of allergy and clinical immunology*. 2014; 133:729–38. e18. [PubMed: 24238646]
37. Tunon-de-Lara JM, Laurent F, Giraud V, et al. Air trapping in mild and moderate asthma: effect of inhaled corticosteroids. *The Journal of allergy and clinical immunology*. 2007; 119:583–90. [PubMed: 17204317]
38. Kim WW, Lee CH, Goo JM, et al. Xenon-enhanced dual-energy CT of patients with asthma: dynamic ventilation changes after methacholine and salbutamol inhalation. *AJR American journal of roentgenology*. 2012; 199:975–81. [PubMed: 23096168]
39. Gur D, Shabason L, Borovetz HS, et al. Regional pulmonary ventilation measurements by xenon enhanced dynamic computed tomography: an update. *Journal of computer assisted tomography*. 1981; 5:678–83. [PubMed: 7298946]
40. Chae EJ, Seo JB, Goo HW, et al. Xenon ventilation CT with a dual-energy technique of dual-source CT: initial experience. *Radiology*. 2008; 248:615–24. [PubMed: 18641254]
- *41. Altes TA, Mugler JP 3rd, Ruppert K, et al. Clinical correlates of lung ventilation defects in asthmatic children. *The Journal of allergy and clinical immunology*. 2016; 137:789–96. e7. This study provides support to the clinical relevance of MR measures of lung ventilation defects in asthmatic children by showing associations between a high burden of ventilation defects and disease severity, medication use, symptoms, airflow obstruction, and markers of atopy. [PubMed: 26521043]
42. Svenningsen S, Kirby M, Starr D, et al. What are ventilation defects in asthma? *Thorax*. 2014; 69:63–71. [PubMed: 23956019]

43. Lutey BA, Lefrak SS, Woods JC, et al. Hyperpolarized ^3He MR imaging: physiologic monitoring observations and safety considerations in 100 consecutive subjects. *Radiology*. 2008; 248:655–61. [PubMed: 18641256]
44. Ohno Y, Nishio M, Koyama H, et al. Asthma: comparison of dynamic oxygen-enhanced MR imaging and quantitative thin-section CT for evaluation of clinical treatment. *Radiology*. 2014; 273:907–16. [PubMed: 25102370]
45. Pennati F, Quirk JD, Yablonskiy DA, et al. Assessment of regional lung function with multivolume $(1)\text{H}$ MR imaging in health and obstructive lung disease: comparison with $(3)\text{He}$ MR imaging. *Radiology*. 2014; 273:580–90. [PubMed: 24937692]
46. Tahir BA, Swift AJ, Marshall H, et al. A method for quantitative analysis of regional lung ventilation using deformable image registration of CT and hybrid hyperpolarized gas/ ^1H MRI. *Phys Med Biol*. 2014; 59:7267–77. [PubMed: 25383657]
- *47. Tahir BA, Van Holsbeke C, Ireland RH, et al. Comparison of CT-based Lobar Ventilation with ^3He MR Imaging Ventilation Measurements. *Radiology*. 2016; 278:585–92. This study demonstrates that CT imaging provides comparable lobar-level ventilation information to MR. CT can be useful to assess ventilation changes due to therapeutic interventions. [PubMed: 26322908]
48. Svenningsen S, Guo F, Kirby M, et al. Pulmonary functional magnetic resonance imaging: asthma temporal-spatial maps. *Academic radiology*. 2014; 21:1402–10. [PubMed: 25300720]
- *49. Thomen RP, Sheshadri A, Quirk JD, et al. Regional ventilation changes in severe asthma after bronchial thermoplasty with $(3)\text{He}$ MR imaging and CT. *Radiology*. 2015; 274:250–9. This article demonstrates that it is possible to quantify lung ventilation defects at bronchopulmonary segmental level before and after therapy using hyperpolarized gas MR imaging. [PubMed: 25144646]

Key Points

Clinically, traditional chest radiography and computed tomography (CT) continue to play a key role in the diagnosis of complications from severe asthma, such as pneumothoraces and bronchiectasis.

Quantitative analysis of CT images has shown that both measures of airway thickening and measures of gas trapping are associated with impairments of lung function, and further advances in dual energy Xenon enhanced CT imaging may improve regional measurements of gas trapping in particular.

Magnetic resonance imaging (MRI) that utilizes hyperpolarized gas has revealed associations between ventilation defects in patients with asthma and both CT measurements of airway remodeling as well as lung function impairment.

The functional nature of hyperpolarized MRI measurements suggests that, combined with quantitative CT analysis, it may provide useful information to both guide and quantify the asthmatics' therapy, but further work is needed before its integration into routine clinical care.

Figure 1. CT scan and hematoxylin-eosin stained bronchial biopsy images from a healthy normal patient (A and C) and patient with severe asthma (B and D). (Epi: epithelium, LR: lamina reticularis) (Reprinted by permission from reference [23])

Figure 2.

a) Association between the baseline ratio of the forced expiratory volume in one second to the forced vital capacity (FEV₁/FVC) and the intermittent ventilation defect percentage of the lung (VDP₁%) as measured by three dimensional tritium (³He) magnetic resonance imaging (MRI). b) Association between the baseline FEV₁/FVC and the persistent ventilation defect percentage of the lung (VDP_p%) as measured by ³He MRI. c) and d) Associations between the FEV₁/FVC after exercise and the VDP₁% and VDP_p% respectively. (Reprinted by permission from reference [48])