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Ventilation Heterogeneity and Its Association with Nodule Formation Among Participants in the National Lung Screening Trial—A Preliminary Investigation

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Abstract

Rationale and Objectives: We have developed a technique to measure ventilation heterogeneity (VH) on low dose chest CT scan that we hypothesize may be associated with the development of lung nodules, and perhaps cancer. If true, such an analysis may improve screening by identifying regional areas of higher risk.

Materials and Methods: Using the National Lung Screening Trial database, we identified a small subset of those participants who were labeled as having a positive screening test at 1 year (T1) but not at baseline (T0). We isolated the region in which the nodule would form on the T0 scan ("target region") and measured VH as the standard deviation of the linear dimension of a virtual cubic airspace based on measurement of lung attenuation within the region.

Results: We analyzed 24 cases, 9 with lung cancer and 15 with a benign nodule. We found that the VH of the target region was nearly statistically greater than that of the corresponding contralateral control region (0.168 [0.110–0.226] vs. 0.112 [0.083–0.203], $p = 0.051$). The % emphysema within the target region was greater than that of the corresponding contralateral

control region (1.339 [0.264–4.367] vs. 1.092 [0.375–4.748], $p = 0.037$). There was a significant correlation between the % emphysema and the VH of the target region ($\rho = +0.437$, $p = 0.026$).

Conclusion: Our study provides the first data in support of increased local VH being associated with subsequent lung nodule formation. Further work is necessary to determine whether this technique can enhance screening for lung cancer by low dose chest CT scan.

Keywords

Linear airspace dimension; Low dose chest CT; Lung cancer; National Lung Screening Trial; Ventilation heterogeneity

INTRODUCTION

Lung cancer is the leading cause of cancer-related death in the United States, accounting for 24% of all cancer related mortality (1). Patients with early stage lung cancer have improved survival when compared to those with late stage disease, implying that early detection could improve mortality (1). Screening for early stage lung cancer by low dose radiation computed tomography (LDCT) has been shown by the National Lung Screening Trial (NLST) to result in a 20% improvement in mortality in a cohort of high-risk individuals (2). However, 96% of all abnormalities picked up by LDCT in the NLST were false positives, leading to additional diagnostic evaluation, complications, health care costs, and anxiety. This high rate of false positives highlights the need for more targeted approaches for implementing lung cancer screening (3–6).

Smoking is responsible for 85% of lung cancers, and is associated with structural abnormalities in the lung characterized by airway inflammation and narrowing and lung parenchymal destruction (7). An important functional effect of these structural changes is the creation of nonuniform gas flow among airways and lung regions, resulting in increased ventilation heterogeneity (VH) (8–10). One of the consequences of increased VH is altered pathways of airflow and particle deposition, which may lead to an increased risk of malignant transformation of airway epithelium and lung cancer (11–15). In particular, high local concentrations of particle deposition may occur at bronchial bifurcations, which may increase the risk for development of lung cancer (12,13,16,17).

Using CT imaging in COPD, unevenness of lung structure can be determined across large regions by measuring the degree of homogeneity of emphysema (18–21). But this approach does not allow more localized assessment of uneven ventilation occurring in the region where lung cancer first appears. We have developed a method to evaluate VH over a small region of lung by relating local attenuation on CT scan to the distribution of the linear dimensions of a virtual cubic airspace (22). Using CT derived measures as biomarkers of increased risk has recently been demonstrated for risk stratification of adenocarcinomas detected by LDCT in the NLST (23). We hypothesize that regions of increased VH may predispose to nodule and/or cancer formation, which, if identified, could allow more focused surveillance of such “hot spots”. We now report the methodology and preliminary results of assessing whether local, increased VH is associated with the subsequent development of a lung nodule.

MATERIAL AND METHODS

NLST Database

We requested access to the NLST demographic and DICOM database from Information Management Services, Inc., via the Cancer Data Access System of the National Cancer Institute (Data Use Agreement NLST-163). The NLST enrolled over 50,000 participants at high risk for lung cancer and randomized them to three annual screenings with low-dose chest CT or single-view posterior-anterior chest radiography (2). As participants were followed through the 3-year study, some of them were found to have positive results at baseline (time zero, T0), 1 year (T1), or 2 years (T2). These positive results were evaluated according to recommended guidelines and were found to either be true positives (lung cancer) or false positives (benign nodules). In this study, we focused our attention on patients who were first noted to have a lung nodule at T1 but not at T0. We were then able to retrospectively measure local VH in the region of lung at T0 that would subsequently develop a lung nodule at T1 (Fig 1).

CT Data Analysis

We asked Information Management Services, Inc., the organization that manages the NLST data base for the Cancer Data Access System of the National Cancer Institute, to identify those participants who were labeled as having a positive screening test at 1 year (T1) but not at baseline (T0) (24). We collected the following data on each participant: age, sex, height, BMI, current vs. former vs. nonsmoker, number of pack-years of smoking, and benign vs. malignant nodule. We used the Chest Imaging Platform of the open source program 3D Slicer (www.chestimagingplatform.org) (25) for all image analysis. The nodule detection algorithm has been previously described and validated (26,27). First, we identified the nodule region of interest (ROI) on the T1 scan (Fig 2—"T1- Nodule ROI"). We then isolated the region of subsequent nodule development on the T0 scan that corresponded to the location of the nodule on the T1 scan (Fig 2—"Target ROI"). This ROI on the baseline scan (T0) was carefully selected by an automated image-based registration algorithm ("BRAINS") in 3D Slicer to define the affine transformation between the T0 and the T1 images. The dimensions of the Target ROI were automatically determined by the algorithm to allow sufficient data for subsequent analysis, and resulted in spheres of variable size between participants, but of the same size between the Target ROI and the contralateral control ROI (see in the following sections). In order to remove blood vessels and other solid structures within the ROI, areas within the ROI with Hounsfield Units (HU) > -600 were excluded from densitometric analysis. Lung attenuation within the Target ROI was measured by the distribution of HU, and the HU's were converted to linear airspace dimension (LAD) by the formula $LAD = \sqrt[3]{-HU/[HU + 1000]}$, from which we calculated the standard deviation of the LAD distribution (LAD-SD) as the measure of VH (22). The higher the LAD-SD, the more variable in size would be the airspaces, representing increased VH in that region. We also calculated the percentage of emphysema within the Target ROI as determined by the %HU < -950.

In order to determine how the VH of the Target ROI where a nodule developed related to VH within other regions of the lung, we measured VH in two control regions of the T0 axial

images: (1) a similarly sized ROI (by volume) as the Target ROI at the same anatomic and gravitational (anterior-posterior) level in the contralateral lung (Fig 2—“T0-Contralateral Control ROI”), and (2) the surrounding complete lung slice containing the nodule, excluding the nodule ROI itself (Fig 2—“T0-Ipsilateral Slice Control ROI”), and a similar contralateral lung slice control ROI (Fig 2—“T0-Contralateral Slice Control ROI”). The slice thickness for all analyses was 2 mm, but the measurements made within the ROI was based on volume and so would nearly always include multiple slices, depending on ROI size.

Data Analysis

All data distributions for outcome measures are reported as medians (interquartile ranges). Within-subject comparisons were made by Friedman Two-Way Analysis of Variance for VH and % emphysema, followed by Wilcoxon Signed-Ranks test for VH of lung slices. Correlations between VH and emphysema were determined by Spearman rank correlation. *p* Values <0.05 were considered statistically significant. All analyses were conducted using SYSTAT Software, Inc., San Jose, CA.

Since our hypothesis was that increased local VH would predispose to nodule formation, the primary analysis was a comparison between the VH of the Target ROI and the T0-Contralateral Control ROI. To account for whether VH in the target ROI was unique or simply a reflection of surrounding VH, we also compared the VH of the Target ROI to the VH of the control lung slice on both the ipsilateral and contralateral sides, again at T0. To determine whether emphysema was related to VH, we compared % emphysema of the Target ROI to that of the T0-Contralateral Control ROI, and % emphysema of the Target ROI to that of the control lung slice on the ipsilateral and contralateral side at T0. Finally, we calculated the correlation between VH and % emphysema in the Target ROI at T0.

This study was considered “Not Human Research” by the Committees on Human Research in the Medical Sciences (CHRM 17–0098), since it involved deidentified data only.

RESULTS

The Information Management Services, Inc. provided us with 355 cancer and control cases according to our inclusion criteria, but after reviewing the first 110 of these, we found only 24 cases that actually had a nodule at T1 but not at T0. Of these, nine had lung cancer and 15 had a benign nodule. Of note, one benign nodule case had three different nodules at T1, so the total sample size was 26 sets of CT data. There were 15 men and nine women, mean (SD) age of 60 years (4), with a smoking burden of 49 pack-years (14). Given the small sample size, the VH of the ROIs for both cancer and benign nodules were combined for this preliminary analysis, particularly because we speculate that the mechanism of nodule formation based on uneven ventilation and particle deposition seems plausible for both benign and cancerous nodules.

Only solid nodules were analyzed by the NLST, and those in our data set ranged in size from 11.6 to 1835 mm³, with a median (25–75 IQR) size of 381 (173–656) mm³. We found that the VH of the Target ROI was greater than that of the corresponding T0-Contralateral Control ROI (median, IQR) (0.168 [0.110–0.226] vs. 0.112 [0.083–0.203], *p* = 0.051),

which was close to, but did not reach, statistical significance (Fig 3). The VH of the Target ROI was less than the surrounding lung slice (T0-Ipsilateral Slice Control ROI): (0.168 [0.110–0.226] vs. 0.409 [0.355–0.525]), $p < 0.001$. However, the VH of the T0-Ipsilateral Slice Control ROI was no different than that of T0-Contralateral Slice Control ROI (0.409 [0.355–0.525] vs. 0.421 [0.352–0.541], $p = 0.412$). We also found that the % emphysema within the Target ROI was greater than that of the T0-Contralateral Control ROI (1.339 [0.264–4.367] vs. 1.092 [0.375–4.748], $p = 0.037$), but no different than that of the ipsilateral lung slice (1.339 [0.264–4.367] vs. 1.004 [0.582–5.336], $p = 0.628$). There was also no difference in % emphysema between the ipsilateral and contralateral control slices at T0 (1.004 [0.582–5.336] vs. 1.629 [0.528–4.392], $p = 0.211$). There was a significant correlation between the % emphysema and the VH of the Target ROI ($\rho = +0.437$, $p = 0.026$).

DISCUSSION

This is the first study to assess the local VH of a region of subsequent nodule formation on CT scan. Our findings show that VH was higher in this region compared to a contralateral control ROI, although this difference did not quite reach statistical significance. Meanwhile, the VH of the lung slice containing the Target ROI was similar to that of the contralateral control lung slice, suggesting that the local difference in VH did not appear to be due to more widespread, surrounding differences in VH. Additionally, there was more emphysema in the Target ROI compared to that of the TO-Contralateral Control ROI, and there was a significant correlation between VH in the Target ROI and the % emphysema in this same region, suggesting that the observed degree of VH was associated with the amount of emphysema.

We believe there is sufficient biological plausibility that VH may be associated with nodule development. A recent study demonstrated that the majority of invasive lung adenocarcinomas occurred in the upper lung zones (28), which may be due, in part, to altered ventilation-perfusion matching resulting in less particulate clearance and immune surveillance. Other studies have also shown that lung cancer is associated with an upper lobe predominance, as well as emphysema and airflow limitation (29–34). We believe the same issues may be relevant to benign nodule formation, since it seems reasonable to speculate that the mechanism of nodule formation based on uneven ventilation and particle deposition may be the similar for both benign and cancerous nodules.

A unifying explanation to these observations may be differences in VH within and between lung regions. Animal studies have shown that alterations in lung structure leads to alterations in particle deposition in the lung (14). Computational models of human airway structure demonstrate that breathing patterns as well as airway geometry affect particle deposition in the lung (15,35–37). In particular, high local concentrations of particle deposition (so-called “hot-spots”) may occur at bronchial bifurcations, which may increase the risk for development of lung cancer (12,13,16,17). Indeed, an autopsy study in humans confirms high concentrations of particulate deposition at airway carinas (13). VH, by definition, involves varying flows of gas moving to different lung regions throughout the respiratory cycle. This will necessarily result in higher than average flows of gas in some regions, which

will lead to an increased probability of inertial impaction of particles (15,36). Combined with the notion of relatively lower perfusion in the upper lung zones, VH in the upper lung zones might be expected to increase the probability of particulate deposition and retention, potentially leading to increased risk of development of lung cancer (28). Recently, the distribution of emphysema, which we found is associated with VH, throughout the lung was found to correlate with lung cancer in HIV-positive smokers screened for lung cancer by CT (19).

Two observations warrant further discussion. First, the difference between the VH of Target ROI and the surrounding lung slice suggests that VH varies throughout the lung. This is why we attempted to select the best ROI for comparison to the Target ROI as an ROI of similar volume in the same gravitational plane (anterior-posterior dimension on the axial view) as the T0—Subsequent T1 Nodule ROI. Second, the correlation between VH and % emphysema suggests that the degree of emphysema contributes to VH. The correlation may be due, in part, to the fact that both VH and emphysema rely on quantitation of parenchymal density by the same variable, HU attenuation. But, in the case of VH, HU density relates to variability in attenuation (SD of airspace sizes), which we envision being due to local differences in regional airflow, whereas in the case of emphysema, HU density relates to absolute attenuation (% of pixels below the absolute threshold of HU -950) due to parenchymal destruction. In addition, we expect that more emphysema should associate with lower VH, not higher VH, since there would be lower variance of HU attenuation. Therefore, we think it is reasonable that emphysema is not the sole determinant of VH, and uneven regional airflow, particularly down to the small airway level, may account for VH as measured by the LAD method. Indeed, Pike et al. have shown that VH measured by MRI exists in ex-smokers without airflow limitation and is associated not only with emphysema but also with airway remodeling, implicating airway abnormalities with VH independent of emphysema (38). If VH is shown to be associated with lung cancer, then VH could be an important CT-derived parameter that may be combined with other known risk factors for the development of lung cancer to derive more accurate predictive risk models (30,31,39,40). In particular, we envision that automated detection of areas of increased VH on screening CT scans could help focus future attention to these regions to increase the sensitivity for early detection of lung nodules. Similarly, perhaps patients with regions of increased VH might undergo more intensive screening than those without increased VH.

There are important limitations to our study. First, we report here early initial findings only, which are based on a small sample size, and this reduced the power of our study to detect a significant difference in VH (although this difference was nearly significant). Further analysis of additional data from the NLST dataset would be necessary to strengthen our findings, and may include additional cases of tumors that formed at T2 but were not seen at T1. Second, the sample size was too small to make meaningful comparisons between benign vs. malignant nodules, but this comparison would be important in order to determine whether VH is uniquely associated with malignant nodule formation, or nodule formation in general. Third, even though the NLST data set is quite unique in providing a large number of CT scans from a given individual over time, there is still variability in acquisition technique (e.g., different equipment, reconstruction parameters) across different study centers, which confounds comparisons across centers. However, if these preliminary findings are validated,

then such variability in techniques may strengthen the generalizability of the findings in the clinical setting. Fourth, further analysis of the ROIs may be enhanced by including different sized ROI's, surrounding shell radii and consequence volumes. While this might mitigate against any small regional variability in VH, it may also dilute any signal that might be present only on a smaller scale. Fourth, we have made the assumption that VH may predispose to nodule formation, but it is possible that VH is a consequence of nodule formation. We feel this possibility is less likely because we specifically focused our attention on the ROI in the T0 scan that did not yet have any visible nodule, at least within the resolution of visual detection by CT scan. Finally, it would be important to confirm that the LAD method is accurately reflecting VH on a local level by using other anatomic techniques to measure regional VH, such as CT texture analysis (41) or MRI (42). Of note, the gold standard functional technique of MBNW would not be helpful because it measures VH on a global level across the entire lungs.

In summary, our study provides the first data in support of increased local VH being associated with subsequent lung nodule formation, and, by extension, possibly cancer. Further work is necessary to confirm this finding and refine the methodology to ensure that it is robust and reliable enough to enhance screening by LDCT by focusing on local areas of higher risk for the development of lung cancer.

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Abbreviations

CHRMS	Committee on Human Research in the Medical Sciences
COPD	chronic obstructive pulmonary disease
HIV	human immunodeficiency virus
HU	hounsfield units
IQR	interquartile range
LDCT	low dose computerized tomography
MRI	magnetic resonance imaging
NLST	National Lung Screening Trial
ROI	region of interest
SD	standard deviation
T0	Time0 (baseline)

T1	Time 1 (1 year)
T2	Time 2 (2 years)
VH	ventilation heterogeneity

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Figure 1. Representative axial CT images of a nodule in the right upper lobe at T1 (right), compared to the same axial level image 1 year prior at T0 (left), in which no nodule is seen, but the region of interest in which the nodule would form is highlighted (solid circle).

Figure 2.

Illustration of CT regions of interest (ROI) analyzed. At Time 1 (T1, right), we identified the nodule (T1 Nodule ROI, solid circle). We then coregistered the scan from baseline (1 year prior, T0, left) and identified the ROI where the T1 nodule would subsequently form (Target ROI, hashed circle). We analyzed the attenuation within this region and used the data to calculate the standard deviation of the linear airspace dimension as a measure of ventilation heterogeneity, as explained in the text. Next, we identified and analyzed a similar sized region at the same horizontal level on the axial view in the contralateral lung at T0 to serve as the T0 Contralateral Control ROI (wavy circle). We also analyzed two other control ROIs at T0 (stippled), one being the ipsilateral slice of lung in which the Target ROI was contained (T0-Ipsilateral Slice Control ROI), and the other being the slice on the contralateral side (T0-Contralateral Slice Control ROI).

Figure 3.

p Values for key comparisons between differences in ventilation heterogeneity of different regions (left) and percent emphysema of different regions (right) on the baseline T0 CT scan. See text for details.