Original Article

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The Effect of Lung Volume on the Size and Volume of Pulmonary Subsolid Nodules on CT: Intraindividual Comparison between Total Lung Capacity and Tidal Volume

전산화단층촬영에서 폐 반고형결절의 크기와 용적에 호흡이 미치는 영향: 개인 내 전폐용량과 일호흡량 간 비교

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Purpose To examine the effect of lung volume on the size and volume of pulmonary subsolid nodules (SSNs) measured on CT.
Materials and Methods A total of 42 SSNs from 31 patients were included. CT examination was first performed at total lung capacity (TLC), and a section containing the nodule was additionally scanned at tidal volume (TV). The diameter and volume of each SSN, as well as the cross-sectional lung area containing the nodule, were measured. The significance of the changes in measurements between TLC and TV within the same individuals was evaluated.
Results The lung area and the diameter and volume of SSNs decreased significantly at TV by 12.7 cm^2, 0.5 mm, and 46.4 mm^3 on average, respectively ($p < 0.001$), compared to those at TLC. Changes in lung area between TV and TLC were positively correlated with the change in SSN diameter ($p = 0.027$) and volume ($p = 0.014$). However, after correction (by considering the change in lung area), the changes in SSN diameter ($p = 0.124$) and volume ($p = 0.062$) were not significantly different.
Conclusion SSN size and volume can be significantly affected by lung volume during CT scans of the same individuals.

Index terms Multidetector Computed Tomography; Total Lung Capacity; Tidal Volume

INTRODUCTION

Subsolid nodules (SSNs), including part-solid nodules (pSNs) and pure ground-glass nodules (GGNs), represent a histological spectrum ranging from preinvasive lesions to invasive lung adenocarcinoma (1). Persistent SSNs that do not resolve for more than 3 months have a high likelihood of malignancy than solid nodules (2). A study reported a malignancy rate of 34% for all SSNs (63% for pSNs and 18% for GGNs), whereas only 7% for solid nodules (3).

More subsolid nodules are being detected because of the broad use of the multi-detector row CT, with reported detection rates of 3%–4% by large scale screening CT studies (4). Accurate and consistent measurement of nodule size is important to identify subtle growth in a short time interval. Furthermore, as with solid pulmonary nodules, the size of SSN matters in terms of malignancy and prognosis prediction (5).

Diameter measurement is widely used in CT lung cancer screening, including the Fleischner society lung nodule recommendations and the Lung Imaging Reporting and Data system (6, 7). However, with thin slice CT and three-dimensional segmentation software readily available, semi-automatic volumetric measurements have been shown to be superior to the diameter measurements (8-10). Although automatic volumetric measurement is known to be accurate and precise, however, it is not easy to distinguish whether the volume change at follow-up is due to actual nodule growth or other factors such as CT parameters and patients' respiration (11).

Previous studies on SSNs concluded that the lung volume can affect significantly the measurements of a pulmonary nodule volume, as the difference between the nodule volume in total lung capacity (TLC) and in tidal volume (TV) was significant (12, 13). However, to the best of our knowledge, there has been no study that investigated the impact of lung volume during CT scan on the nodule volume measurement within the same individual. Therefore, the aim of this study was to examine the effect of lung volume on SSN's size and volume measured on CT by comparing them between TLC and TV within same individuals.

MATERIALS AND METHODS

PATIENTS AND NODULES

This retrospective study was approved by the Institutional Review Board of National Health Insurance Service Ilsan Hospital (IRB No. NHIMC 2021-03-056), and the informed consent from the participants was waived. We enrolled 31 patients who were followed up for known SSNs between December 2014 and March 2021. Of the enrolled 31 patients, 24 (77.4%), 5 (16.1%), 1 (3.2%), and 1 (3.2%) underwent 1, 2, 3, and 4 CT scans, respectively. Only one patient had two SSNs, and the remaining patients had single SSNs. Therefore, the final study subjects consisted of 42 SSNs in 31 patients.

CT IMAGING

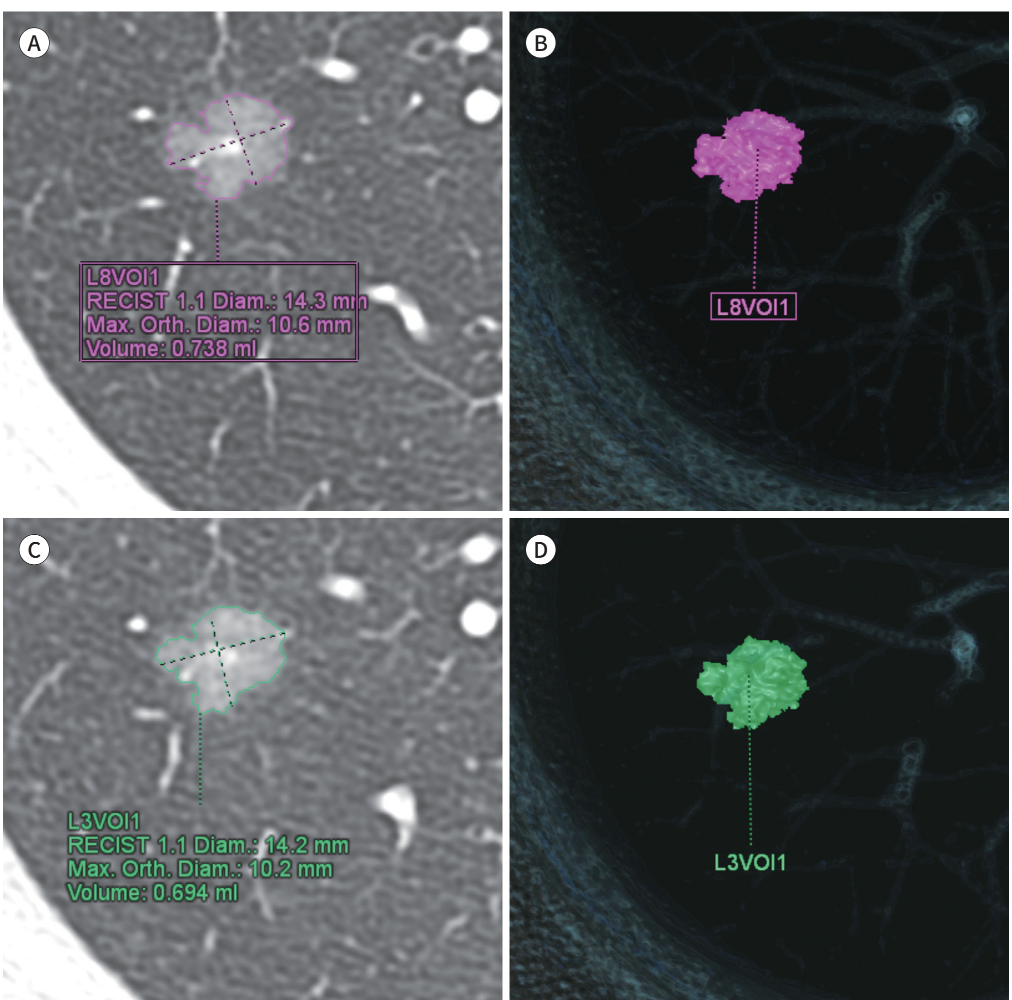
All CT examinations were performed using the same 64-slice dual-source CT (SOMATOM Definition Flash, Siemens Healthcare, Erlangen, Germany) with the following parameters: a fixed tube voltage of 120 kVp with automated tube current modulation, slice collimation of

64 × 0.6 mm, and spiral pitch factor of 0.6, and table feed per rotation of 23 mm. After breathing instructions, the full length of thorax—from the lower neck to the upper abdomen—was first scanned at full inspiration (i.e., at TLC) in supine position with elevated arms, and a section containing SSNs was additionally scanned during tidal or resting breathing (i.e., at TV) in the same scan parameters and position. Of the 42 SSNs, 12 (28.6%) were scanned after a body-weight-adapted dose of iodinated contrast medium was injected intravenously (Iobitridol 300 mg/mL; Guerbet, Seoul, Korea). Images were reconstructed in axial view with a section thickness of 1.5–2.0 mm using both soft tissue (B40f) and sharp (B70f) kernels.

IMAGE ANALYSIS

On our picture archiving communication system (Centricity, GE Healthcare, Milwaukee,

Fig. 1. Measurement of the diameter, volume, and attenuation of a SSN in a 60-year-old female at total lung capacity (A, B) and tidal volume (C, D).
A-D. On the axial slices where the SSN's longest diameter becomes largest, region of interests outlining the nodule are drawn while taking care not to include large blood vessels to measure the nodule's volume (B, D) as well as attenuation. Note that the SSN's volume is higher at total lung capacity (A, B) than at tidal volume (C, D) despite the similar measured diameters.
RECIST = response evaluation criteria in solid tumors, SSN = subsolid nodule



WI, USA), a radiologist with more than 15 years of experience in interpreting chest CT (S.J.R.) reviewed the TLC and TV images in the lung window setting to select the axial slice showing the SSN's largest diameter and determined the SSN's location and measurement direction (Fig. 1). Using the selected images, the radiologist measured the longest diameter of the SSN on both at TLC and TV twice. For each SSN, the two diameter measurements were averaged and used as the final measurement result. In addition, on the same images, the radiologist drew a region of interest outlining the nodule while taking care not to include large blood vessels and measured the attenuation in Hounsfield Unit (HU) for 30 lesions scanned without contrast enhancement. Lastly, after transferring the images to a workstation, the radiologist used a three-dimensional software program (Syngo.via, Siemens Healthineers, Erlangen, Germany) to measure the SSN's volume and the cross-sectional area of the ipsilateral lung where the center of the lesion was located. The processes of measuring the SSN's attenuation and volume and the lung's area were repeated three times at intervals of several days, and the three measurements for each SSN were averaged to be used as the final measurement result.

STATISTICAL ANALYSIS

The change in various measurements between TLC and TV was calculated by the following formula: (TLC measurement-TV measurement)/TV measurement × 100. To compare the tumor size while taking into consideration the change in lung area, the corrected TV diameter and volume according to the decreased lung area were calculated by the following formula: corrected TV diameter = TV diameter × (TLC lung area/TV lung area). Paired *t* test was used to the significance of change in diameter, volume, and attenuation measurements between TLC and TV. Correlation between the change in lung area and the change in measurements was calculated and represented by Pearson's correlation coefficient rho. The linear relationship between lung area and measurements was fit and represented using linear regression. All analyses were performed using R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

PATIENTS AND NODULES

The characteristics of the patients and nodules are summarized in Table 1. Of the 31 patients, 13 and 18 were male and female, respectively, with a mean age of 59.3 years (range, 26–78 years). Pathologic results were obtained in 11 out of 31 patients. Carcinoma was diagnosed in 10 patients (90.9%) by fine needle aspiration or video-assisted thoracoscopic surgery: 8 lepidic-predominant adenocarcinomas, 1 minimally invasive adenocarcinoma, and 1 bronchiolo-alveolar carcinoma. In the remaining one patient who underwent 2 CT scans, a benign inflammatory lesion was confirmed after transbronchial lung biopsy. All the 42 nodules were round or oval with definite margins. Based on the radiologic findings (14), 33 (78.6%) and 9 (21.4%) were GGNs and pSNs, respectively.

RADIOLOGIC FINDINGS AT TV VS. TLC

The nodule diameter was measured for all the SSNs, but the nodule volume was measured

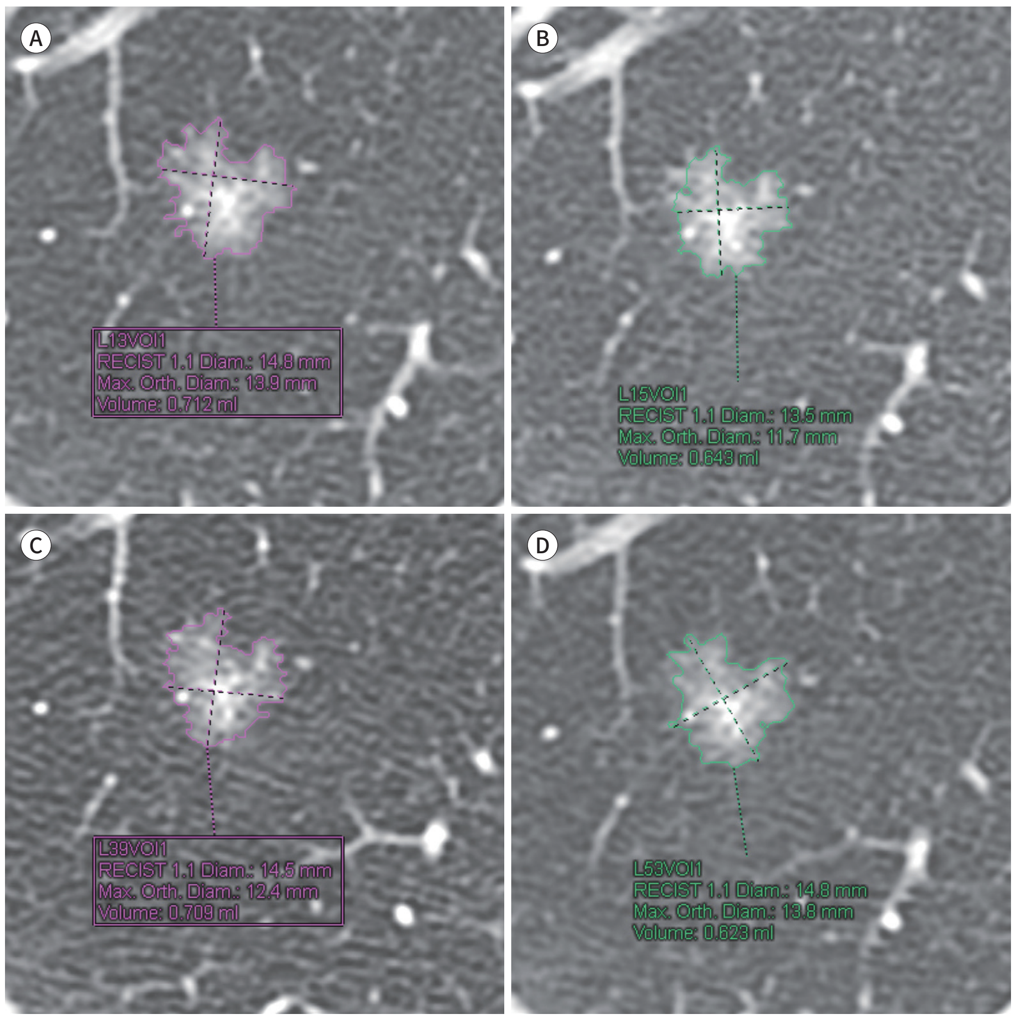
Table 1. Characteristics of Patients and SSNs

Per Patient	
No. of patients	31
Age, mean (range)	59.3 (26–78)
Sex, %	
Male	13 (41.9)
Female	18 (58.1)
No. of SSNs, %	
1	30 (96.8)
2	1 (3.2)
No. of CT scans, %	
1	24 (77.4)
2	5 (16.1)
3	1 (3.2)
4	1 (3.2)
Per Nodule	
Total number of scanned SSNs	42
Diameter at tidal volume, mm	
Mean	13.4
Standard deviation	4.7
Range	6.8–25.9
Diameter at total lung capacity, mm	
Mean	13.9
Standard deviation	4.9
Range	7.1–27.3
Type, %	
Pure ground-glass nodules	33 (78.6)
Partial-solid nodule	9 (21.4)
Pathologic diagnosis, %	
Adenocarcinoma	10 (23.8)
Inflammatory	2 (4.8)
Not determined	30 (71.4)

SSN = subsolid nodule

in 37 (88.1%) because the software tool failed to segment the other 5 nodules accurately. In addition, the attenuation was measured only in 30 (71.4%) of the SSNs that had been scanned without contrast injection to exclude the potential impact of contrast-enhancement on the attenuation measurement. The mean (range) of the included SSNs were 13.9 (7.1–27.3) mm at TLC and 13.4 (6.8–25.9) mm at TV (Table 1). Compared to when scanned at full inspiration (i.e., TLC), during tidal breathing the lung area and the diameter and volume of the same SSN decreased significantly by 12.7 cm^2, 0.5 mm, and 46.4 mm^3 on average, respectively, and the attenuation increased by 55.9 HU on average (Fig. 2 and Table 2; $p < 0.001$ for all comparisons). The difference in size measurement was more prominent with larger nodules (Table 2).

Fig. 2. A case of SSN in a 56-year-old female who underwent two serial CT scans wherein the nodule could be mistakenly determined to have grown.
A, B. At the initial CT scan, the volume of the SSN was 0.712 mL at TLC (A) and 0.643 mL at TV (B).
C, D. At the six-month follow-up, the volume was 0.709 mL at TLC (C) and 0.623 mL at TV (D). When comparing the two CT scans under the same respiratory state, it is obvious that the SSN did not grow. However, if the volume of the SSN, which was measured at TV initially, had been measured at TLC at the follow-up CT scan, it would have been determined to have grown for six months from 0.643 mL to 0.709 mL.
RECIST = response evaluation criteria in solid tumors, SSN = subsolid nodule, TLC = total lung capacity, TV = tidal volume



CHANGE IN NODULE SIZE AND ATTENUATION ACCORDING TO LUNG AREA

The change in lung area between TV and TLC showed positive correlations with the change in the SSN's diameter (rho = 0.341; $p = 0.027$) and that in volume (rho = 0.401; $p = 0.014$) (Fig. 3). Based on the linear regression line fitted to the data, the diameter and volume increased by 1.1% and 2.6% on average as the lung area increased by 10%. However, after being corrected by taking into consideration the change in lung area, the mean diameter and volume of the SSNs were not significantly different between TV and TLC (Table 2; $p = 0.124$ and $p = 0.062$, respectively).

Table 2. Lung Area and the Diameter and Volume of SSNs at Tidal Lung Volume vs. Total Lung Capacity

	Total Lung Capacity	Tidal Volume	Difference	*p*-Value
Lung area, cm^2	111.2 (33.6)	98.5 (30.6)	-12.7 (9.0)	< 0.001
SSN attenuation, HU	-575.2 (86.2)	-519.3 (104.5)	55.9 (42.7)	< 0.001
Without correction				
SSN diameter, mm				
All	13.9 (4.9)	13.4 (4.7)	-0.5 (0.4)	< 0.001
Small (< 10 mm)	9.2 (0.9)	9.0 (0.9)	-0.2 (0.1)	
Medium (10–15 mm)	12.5 (1.5)	12.1 (1.6)	-0.4 (0.4)	
Large (> 15 mm)	20.1 (4.6)	19.4 (4.6)	-0.7 (0.6)	
SSN volume, mm^3				
All	660.7 (538.5)	614.3 (513.2)	-46.4 (34.5)	< 0.001
Small (< 10 mm)	259.6 (60.5)	236.5 (59.2)	-23.1 (10.1)	
Medium (10–15 mm)	593.7 (346.3)	550.7 (340.9)	-43.0 (29.0)	
Large (> 15 mm)	1425.0 (624.6)	1335.9 (590.0)	-89.1 (35.5)	
With correction according to the decreased lung area				
SSN diameter, mm (corrected)				
All	13.9 (4.9)	14.0 (4.7)	0.1 (0.4)	0.124
Small (< 10 mm)	9.2 (0.9)	9.4 (0.9)	0.2 (0.1)	
Medium (10–15 mm)	12.5 (1.5)	12.5 (1.6)	0 (0.4)	
Large (> 15 mm)	20.1 (4.6)	20.2 (4.6)	0.1 (0.5)	
SSN volume, mm^3 (corrected)				
All	660.7 (538.5)	682.1 (503.6)	21.4 (67.6)	0.062
Small (< 10 mm)	259.6 (60.5)	268.9 (59.2)	9.3 (10.3)	
Medium (10–15 mm)	593.7 (346.3)	562.7 (340.9)	9.0 (46.2)	
Large (> 15 mm)	1425.0 (624.6)	1499.1 (590.0)	74.1 (128.4)	

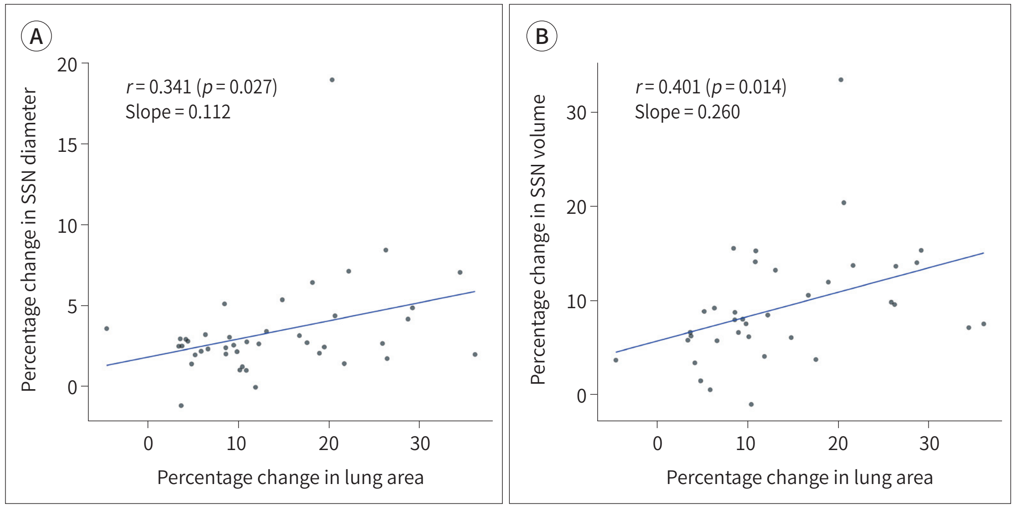
Values in cells are mean (standard deviation).
HU = Hounsfield unit, SSN = subsolid nodule

DISCUSSION

The results of this study demonstrate that the size or volume of SSNs measured on CT can be significantly affected by the change in lung volume (i.e., between TLC and TV). Thus, we must be careful not to interpret the increase in size or volume of SSNs caused by lung volume change as a true nodule growth (Fig. 2). This is further supported by our findings that the mean diameter and volume of the SSNs were not significantly different between TV and TLC, after being corrected by taking into consideration the change in lung area.

Among persistent SSNs, pSN with solid components inside is highly likely to be microinvasive lung adenocarcinoma or invasive lung adenocarcinoma, while GGNs are more likely to be benign lesions such as lymphoproliferative diseases, organized pneumonia, or interstitial fibrosis than lung cancer precursors such as atypical adenomatous hyperplasia or adenocarcinoma (15). In this study, of 11 cases where biopsies were performed, 10 (90.9%) were confirmed as malignant; this high malignancy rate is because those lesions were highly selected ones with large nodule sizes (average, 17.1 mm; range, 10.2–26.9 mm).

Fig. 3. Scatterplot with a line of best fit of the change in lung area between tidal volume and total lung capacity as a function of the diameter (A) and volume (B) of the SSNs.
SSN = subsolid nodule



The Fleischer Society recommends follow-up for SSNs with a diameter of 6 mm (100 mm^3 in volume) or more at regular intervals for 5 years (14). The most important morphologic factors that determine specific follow-up practices are the change in nodule size or volume. For the measurement of nodules including SSN, there are two conventional methods: one-dimensional long diameter measurement proposed by response evaluation criteria in solid tumors and two-dimensional measurement method proposed by the Fleischner Society (16, 17). In current practice, these two methods are being used widely mainly due to its convenience. However, the disadvantages of these methods include the poor reproducibility and reliability due to large variability, especially when the nodule boundary is unclear (11, 18).

Recently, there have been many studies on methods of measuring the volume of nodules in a semi-automated or automated manner using software. This volumetric measurement is recognized as a method with a higher accuracy than the diameter measurement method because it has better reproducibility due to low intra- or inter-observer variability and higher specificity or positive predictive value (11, 19-22). However, even with the volumetric measurement methods, there are many variables that affect the measurements and thus make it difficult to distinguish whether the change in nodule size or volume is due to actual nodule growth or other factors related to the patient, image acquisition and reconstruction, or measurement software (5, 16). Among the factors related to patients, it is known that fluctuations in respiration volume during scanning are highly likely to affect the measured nodule size or volume. In a previous study that measured the volume of solid nodules during inspiration and expiration, the nodule was measured larger in expiration, possibly due to alveolar collapse around the nodule added to the nodule volume (12). On the other hand, in another study on solid nodules, the nodule volume was significantly larger in inspiration than in expiration, and they concluded that the degree of lung expansion may also increase the measured volume (13).

Unlike solid nodules, SSNs pathologically have areas filled with air inside (i.e., alveoli maintained within the nodules), which means that they are more likely to be affected by respiration in a larger extent than solid nodules because the air-filled areas will also expand and contract by respiration. This speculation is supported by our results, the significant differences in SSN size or volume and attenuation between TLC and TV. Furthermore, we found that the volume change was correlated with the change in lung cross-sectional area better than the diameter change, which suggests that the volumetric method may be a better marker of total lung volume. Nowadays, three-dimensional volume measurement can be performed easily using software used in routine practice.

There are limitations in this study. First, the number of study subjects is small, so further validation is warranted through a larger scale study. Second, to reduce the radiation exposure, additional CT scans were performed only on lung portions where the nodules are located, which forced us to use the lung area instead of the entire lung volume. Lastly, since only nodules with clear lesion boundaries were selected, which may have led to selection bias.

In conclusion, the difference in lung volume according to TLC and TV may significantly affect the measurements of volume and CT attenuation of SSNs within same individuals. Therefore, when SSNs show interval increases in size, the possible effects of lung volume by respiration must be considered before concluding that the nodule has grown.

Author Contributions

Conceptualization, R.S.J.; data curation, R.S.J.; formal analysis, all authors; investigation, all authors; methodology, A.C., R.S.J.; project administration, R.S.J.; software, A.C., R.S.J.; supervision, A.C., R.S.J.; visualization, L.H., A.C.; writing—original draft, all authors; and writing—review & editing, all authors.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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전산화단층촬영에서 폐 반고형결절의 크기와 용적에 호흡이 미치는 영향: 개인 내 전폐용량과 일호흡량 간 비교

이현지[1] · 안찬식[2] · 유석종[2]*

목적 전산화단층촬영에서 호흡에 의한 폐 용적의 변화가 폐 반고형결절의 크기와 용적에 미치는 영향을 알아보고자 한다.

대상과 방법 총 31명의 환자에서 42개의 반고형결절이 연구에 포함되었다. 먼저 총 폐활량 상태에서 전산단층화촬영을 시행 받은 후, 결절이 포함된 부분만 일호흡용적 상태에서 추가로 촬영하였다. 각각의 반고형결절의 직경과 용적을 측정하였고, 전체 폐 용적은 결절의 중심이 있는 동측 폐의 단면적으로 추정하였다. 동일한 개인 내에서 총 폐활량과 일회 호흡량 간 측정값 변화의 유의성을 통계적으로 평가하였다.

결과 총 폐활량 상태와 비교하였을 때, 일회 호흡용적 상태에서 폐 단면적은 평균 12.7 cm^2, 반고형결절의 직경 및 용적은 평균적으로 각각 0.5 mm와 46.4 mm^3 감소하였다($p < 0.001$). 총 폐활량 상태와 일호흡량 상태 간 폐 면적 변화는 반고형결절의 직경 변화(rho = 0.341; p = 0.027) 및 부피 변화(rho = 0.401; p = 0.014)와 유의한 양의 상관관계를 보였다. 그러나 폐 용적의 변화를 고려하여 보정한 후에는 반고형결절의 평균 직경과 부피가 총 폐활량 상태와 일호흡량 상태 간 유의한 차이가 없었다(각각 p = 0.062, p = 0.124).

결론 전산화단층촬영에서 측정한 반고형결절의 크기와 용적은 동일한 환자 내에서도 촬영 당시의 폐 용적에 유의한 영향을 받는다.

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