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Influence of contrast agent on artificial intelligence-based CT low attenuation volume percentage measurement

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Abstract

Background: Low attenuation volume percentage (LAV%) has been identified as a quantitative imaging biomarker for emphysema with good correlation with spirometry. The influence of intravenous contrast agent on LAV% and its correlation with spirometry is not well known.

Purpose: To evaluate the influence of intravenous contrast agent on artificial intelligence (AI)-based LAV% in correlation with spirometric Tiffeneau-Pinelli Index (TI).

Material and Methods: In a retrospective study, two groups of 47 patients (mean age 68.04 ± 12.64 and 67.89 ± 11.54 years) with either non-enhanced chest computed tomography (CT) or contrast-enhanced CT were compared. Using an AI-based software, LAV% was quantified using a threshold <−950 HU. TI was calculated from spirometry and pathologic airway obstruction was considered with a TI <70. The effect of contrast agent on LAV% and the relationship between TI and LAV% was analyzed. Correlation coefficients between TI and LAV% were compared for both groups.

Results: Patients with non-enhanced CT had a mean LAV% of 9.07 ± 7.53. Of them, 22 patients had a TI <70% and 25 patients a TI ≥70%. Patients with contrast-enhanced CT had a mean LAV% of 6.54 ± 4.62. Of them, 20 patients had a TI <70% and 27 patients had a TI ≥70%. Contrast agent did not show a major effect on LAV% ($P = 0.099$) and the relationship between TI and LAV% ($P = 0.88$). In both groups, a significant correlation between TI and LAV% was found ($\rho = -0.317$ for non-enhanced CT; $\rho = -0.514$ for contrast-enhanced CT). Difference between correlation coefficients was insignificant.

Conclusion: Our findings suggest that contrast agent does not influence LAV% nor its correlation with TI.

Keywords

Artificial intelligence, chest computed tomography, low attenuation volume percentage, contrast enhancement

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Introduction

Chronic obstructive pulmonary disease (COPD) is the most common chronic respiratory disease and the third leading cause of death in the world (1,2). One of its pathologic hallmarks is pulmonary emphysema. It is defined as an abnormal, permanent enlargement of airspaces beyond the terminal bronchioles accompanied by the destructive changes of alveolar walls (3). On spirometry, this is usually associated with the decrease in Tiffeneau-Pinelli Index (TI), which is the ratio of forced expiratory volume in 1 s (FEV1) over forced vital capacity (FVC) (4). On chest computed tomography (CT), the pathologic changes of emphysema are directly reflected as areas of low attenuation and can be quantified by determining the proportion of voxels below a density threshold of −950 Hounsfield units (HU), also known as the percentage of low attenuation volume (LAV%) (5–7). This threshold has shown good correlations with morphologic emphysema and lung function

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tests and can therefore be regarded as valid for quantification of emphysema on chest CT (8,9).

Recently, an artificial intelligence (AI)-based software being capable of fully automatically generating LAV% values has been cleared by the U.S. Food and Drug Administration (FDA). In an initial study, the AI-based LAV% derived from non-enhanced chest CT correlated very well with spirometric parameters, indicating that the software is able to predict the decrease in lung function and emphysema severity (10). In contrast to manual or semi-automated segmentation algorithms, which often require time-consuming postprocessing of CT data, this AI-based software allows for a fully automatic and human independent LAV% quantification with color-coded emphysema visualization. Thus, it is more suitable for being integrated into the daily clinical workflow. This might enhance the diagnosis of emphysema in unselected patient groups.

In the past, non-enhanced CT is preferred for emphysema quantification, as the distribution of intravenously administered contrast agent in maintained pulmonary capillaries of emphysematous lungs potentially could shift the density toward higher HU values, and thus reduce the detection of LAV%. However, only limited data exist on how the correlation between LAV% and spirometric parameters is affected by the presence of intravenous contrast agent (11–13).

Therefore, the aim of this retrospective study was to assess the influence of intravenous contrast agent on threshold-based LAV% measurement and the correlation with TI using an AI-based software.

Material and Methods

Patient population

By a database query of the hospitals information system (Orbis, Dedalus; DH Healthcare GmbH, Bonn, Germany) we retrospectively gathered data on any patient (n = 47) between January 2018 and June 2020 who received unenhanced chest CT as well as a valid spirometry exam within a hospitalization time of four weeks. For comparison, this group was matched with an equally sized group taken from a pool of 251 patients who received contrast-enhanced chest CT but otherwise fulfilled the same criteria. Hence, our entire study population consisted of 94 patients (63 men [67.02%], 31 women [32.98%]; mean age = 67.97 ± 12.04 years). Matching was based on age using an R package called MatchIt (14), which uses non-parametric preprocessing to optimize the process of pairing, subset selection, and subclassification. The method of optimization was based on the minimization of the sum of absolute pairwise distances in the matched sample.

Upon reviewing the clinical reports, we payed special attention to absence of diagnosis of bronchial asthma, as it might falsely contribute to a decrease in TI not associated with COPD and emphysema. Furthermore, the CT scans were reviewed for the absence of severe artifacts that might interfere with LAV% quantification. Further exclusion criteria were not undertaken.

Descriptive data were collected regarding sex, age, height, weight, body mass index (BMI), and the number of days that passed between spirometry and CT acquisition.

This study was approved by the Ethics Commission II of the University Medical Center Mannheim of the University of Heidelberg (Reference number 2020-864R).

Spirometry protocol

Lung function was measured in accordance to European Respiratory Society criteria (Masterscreen Body Jaeger spirometer, Jaeger, Würzburg, Germany) (15).

The values that were evaluated included FEV1 and FVC in liters as well as TI (FEV1/FVC) in percent. A TI $\geq$70% was considered physiologic whereas a TI <70% was considered to reflect pathologic obstruction. However, reversibility with bronchodilation was not checked and information on bronchodilator medication was not available.

All spirometry exams met the criteria of quality and reproducibility.

CT acquisition protocol

All CT scans were performed on a 128-channel CT scanner (Somatom Definition AS+; Siemens Healthineers, Erlangen, Germany). All chest CT studies were acquired during breath-hold at end inspiration with a collimation of 128 × 0.6 mm, a tube voltage of 120 kV, and a reference tube current of 75 mAs using automatic tube current modulation. Axial slices of 2 mm were reconstructed using sinogram affirmed iterative reconstruction (SAFIRE) with a sharp kernel (I70) according to our institutional clinical standards.

In contrast-enhanced CT scans, a volume of 60 mL of iodinated contrast agent (Imeron 400; Bracco Imaging S.p.A., Milan, Italy) was injected using a power injector with an injection rate of 4 mL/s and followed by a saline chaser of 30 mL. Scans were automatically started using bolus triggering in the ascending aorta. This protocol is the institutional standard for contrast-enhanced systemic arterial phase chest CT, e.g. used for tumor staging.

CT analysis

A commercially available AI software (AI-RAD Companion Chest CT; Siemens Healthineers, Erlangen, Germany) was used for LAV% quantification in this study. The AI software has been recently approved and cleared by the U.S. FDA with FDA-clearance reference "AI-Rad Companion Engine (K183272), Pulmonary

(K183271) and Cardiovascular (K183268) modules." Its principle has been previously described in detail elsewhere (10,16,17). All chest CT scans were sent to a cloud platform (Teamplay digital health platform; Siemens Healthineers, Erlangen, Germany) that deploys the AI software. A deep convolution image-to-image network was used for lung segmentation. The entire 3D CT volumes serve as input for the algorithm. As output, probability maps are generated that indicate how likely voxels belong to a specific lung lobe. In a preprocessing step of lung segmentation, the carina of trachea is automatically identified as a landmark in order for the algorithm to be executed (18). Pulmonary blood vessels are not excluded by the software due to their positive HU value, which does not contribute to LAV%. Furthermore, airways are not removed by the software, as only a slight effect can be expected considering that the volume of airways is approximately 0.5% of the whole lung volume (19).

LAV%, which represents the percentage of lung voxels with attenuation below a threshold of −950 HU was automatically calculated by the software. In the software documentation, non-enhanced data are not considered a prerequisite (20). AI-based lung segmentation was checked for accuracy by a specialized chest radiologist.

Statistical analysis

Statistical analyses were performed using R statistical software version 4.0.4 (21).

Categorical data are presented as counts and percentages. Quantitative data are expressed as mean ± SD and median with interquartile range (Q1–Q3). Normality of data was assessed using Shapiro–Wilk test.

Differences between both patient groups were calculated with a chi-square test of independence for qualitative data and Mann–Whitney test for quantitative data.

Furthermore, we divided our whole study population into patients with obstruction (TI <70%) and without obstruction (TI ≥70%). The effect of these groups on LAV% as well as interaction with contrast enhancement was tested with aligned-rank analysis of variance (ANOVA), a non-parametric factorial analysis (22,23).

Correlations between TI and LAV% were calculated with the Spearman's correlation rank test. In all calculations, a P value <0.05 was considered to be statistically significant.

Results

Detailed characteristics and differences between the groups with non-enhanced and contrast-enhanced CT are presented in Table 1. None of the characteristics showed a significant difference with the exception of the time interval between spirometry and CT scan acquisition ($P = 0.016$), with a shorter interval in the group of patients with contrast-enhanced CT.

LAV% quantification and spirometry results

Patients who received non-enhanced CT scan had a mean LAV% of 9.07% ± 7.53% and a mean TI of 69.31% ± 11.77%. Of this group, 22 patients had a TI <70% and 25 patients a TI ≥70%.

Patients who received a contrast-enhanced CT scan had a mean LAV% of 6.54% ± 4.62% and a mean TI of 71.24% ± 11.27%. Of them, 20 patients had a TI <70% and 27 patients a TI ≥70%.

The differences of LAV% and TI results between the two groups were found to be insignificant ($P = 0.5$; $P = 0.11$) and are provided in Table 1. The effect size of LAV % between the two groups was r = 0.152.

Effect of TI and contrast enhancement on LAV%

In our aligned-rank ANOVA, we analyzed the effect of obstruction (TI <70%) or no obstruction (TI ≥70%) on LAV%, the effect of using contrast agent on LAV%, and the interaction of contrast agent on the relationship between TI and LAV% (Table 2).

LAV% was significantly influenced by whether patients had a TI <70% or ≥70% ($P < 0.001$). The group with a TI <70% had significantly higher LAV% values than the group with a TI ≥70%.

The use of contrast agent did not show any significant effect on LAV% ($P = 0.099$). Furthermore, we found that contrast enhancement did not significantly affect the relationship between TI and LAV% ($P = 0.88$).

Correlation between TI and LAV%

Spearman's correlation test revealed a significant correlation between TI and LAV% for both non-enhanced and contrast-enhanced scans (Fig. 1). In the group of patients with non-enhanced scans, a weak correlation was found ($\rho = -0.317$, $P = 0.036$), whereas in the group of patients with contrast-enhanced scans a moderate correlation ($\rho = -0.514$, $P = 0.00064$) was noticed.

Discussion

Although numerous studies have demonstrated the feasibility of CT-based emphysema quantification as well as good correlation with spirometric lung function tests, this application has not yet been well established in clinical routine. One potential reason is the often-required time-consuming postprocessing of chest CT data associated with manual or semi-automated segmentation algorithms. In contrast, the AI-based software used in this study allows for a fully automaticity and human independent LAV% quantification. The results are automatically transferred from the cloud platform to the PACS and can be directly integrated into the reading process. Using dedicated

Table 1. Characteristics of study population as well as AI-based LAV% quantification and spirometry results.

Characteristics and results	All patients (n = 94)	Non-enhanced (n = 47)	Contrast-enhanced (n = 47)	*P* value*
Sex				
Female	31/94 (32.98)	17/47 (36.17)	14/47 (29.79)	0.5
Male	63/94 (67.02)	30/47 (63.83)	33/47 (70.21)	
Age (years)	67.97 ± 12.04	68.04 ± 12.64	67.89 ± 11.54	>0.9
	69.50 (60.00–77.75)	71.00 (60.50–77.50)	69.00 (60.00–77.50)	
Height (m)	1.71 ± 0.10	1.70 ± 0.11	1.72 ± 0.10	0.6
	1.71 (1.63–1.79)	1.70 (1.64–1.79)	1.71 (1.63–1.79)	
Weight (kg)	80.08 ± 18.46	79.66 ± 16.78	80.51 ± 20.17	>0.9
	26.37 (23.42–29.86)	78.00 (68.10–88.00)	77.00 (69.50–88.50)	
BMI (kg/m^2)	27.41 ± 6.18	27.42 ± 4.87	27.40 ± 7.31	0.4
	26.37 (23.42–29.86)	26.64 (24.01–29.65)	25.97 (22.61–29.89)	
Time (days)†	4.11 ± 4.71	5.43 ± 5.53	2.79 ± 3.28	0.016
	2.50 (1.00–5.00)	4.00 (1.00–8.50)	1.00 (1.00–4.50)	
FEV1 (L)	1.97 ± 0.86	1.92 ± 0.84	2.02 ± 0.89	0.6
	1.94 (1.31–2.50)	1.71 (1.23–2.54)	2.09 (1.33–2.42)	
FVC (L)	2.79 ± 1.10	2.74 ± 1.00	2.83 ± 1.20	0.8
	2.67 (1.91–3.76)	2.39 (1.92–3.59)	2.73 (1.91–3.83)	
TI (%)	70.27 ± 11.50	69.31 ± 11.77	71.24 ± 11.27	0.5
	71.71 (63.11–78.53)	70.55 (62.99–76.41)	72.01 (63.75–79.74)	
TI <70% (n)‡	42	22	20	0.7
TI ≥70% (n)	52	25	27	
LAV%	7.81 ± 6.34	9.07 ± 7.53	6.54 ± 4.62	0.11
	6.65 (3.42–9.75)	6.80 (3.90–11.85)	6.20 (2.45–8.90)	

Values are given as n (%), mean ± SD, or median (IQR).
**P* value representing the differences in results between the two study groups.
†Number of days between spirometry and CT scan acquisition.
‡Number of patients with TI <70% or ≥70%.
AI, artificial intelligence; BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; LAV%, low attenuation volume percentage; TI, Tiffeneau-Pinelli Index.

Table 2. Influence of TI and contrast-enhancement on AI-based LAV% quantification.

TI <70%/≥70%	Contrast enhancement	LAV%	*P* value
<70%	Yes	9.01 ± 5.09	TI <70%/≥70% <0.001*
		8.9 (6.00–11.53)	
<70%	No	11.73 ± 9.40	Contrast = 0.099†
		8.9 (6.20–13.50)	
≥70%	Yes	4.71 ± 3.27	Interaction term = 0.88‡
		5.1 (1.65–7.10)	
≥70%	No	6.74 ± 4.38	
		5.2 (3.40–10.0)	

Values are given as mean ± SD or median (IQR).
*Main effect of TI <70% or ≥70% on LAV%.
†Main effect of contrast enhancement on LAV%.
‡Effect of contrast enhancement on correlation between TI and LAV%.
AI, artificial intelligence; LAV%, low attenuation volume percentage; TI, Tiffeneau-Pinelli Index.

AI-based software several quantitative parameters can be fully automated extracted from imaging studies performed in clinical routine (10,24,25).

As chest CT in clinical practice is commonly performed using an intravenous contrast agent, we aimed to evaluate whether contrast-enhanced CT can be used for the measurement of LAV% using an AI-based software. As expected, we found a slight decrease of LAV% in contrast-enhanced exams that can be attributed to an increased density of the pulmonary parenchyma caused by presence of contrast within the pulmonary vasculature and alveolar capillaries. However, this slight decrease in

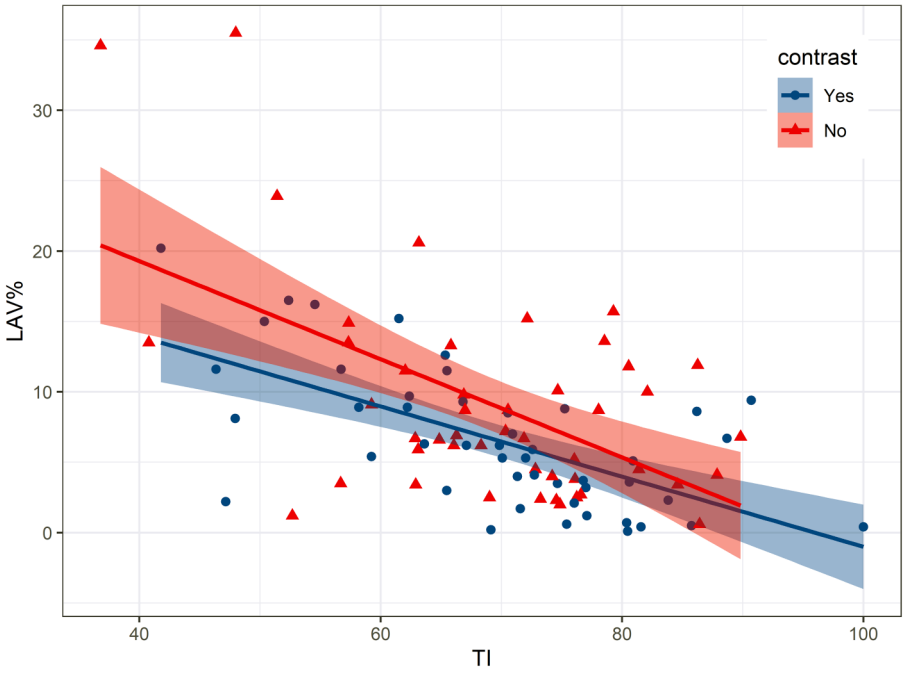

Fig. 1. Graphical illustration of the correlation between percentage of LAV% and TI. The red graph depicts the correlation for patients who underwent non-enhanced CT ($\rho = -0.317$). The blue graph shows the correlation for patients who received contrast-enhanced CT ($\rho = -0.514$). The lighter blue and red areas reflect the corresponding confidence intervals. The difference between correlation coefficients was statistically insignificant. CT, computed tomography; LAV%, low attenuation volume percentage; TI, Tiffeneau-Pinelli Index.

LAV% was not found to be statistically significant. Furthermore, our aligned-rank ANOVA showed that the effect of contrast agent on correlation between TI and LAV% is negligible. Regardless of the presence of intravenous contrast agent, a significant correlation between TI and LAV% was found, indicating a correlation between CT-based emphysema assessment and lung function. In addition, the observed small effect size of LAV% ($r = 0.152$) between the non-enhanced and contrast-enhanced CT groups supports the overall low effect of contrast enhancement. A hypothesis to explain these findings could be that destructive changes of alveoli in emphysema can be associated with loss of lung capillaries, which, in turn, may decrease the significance of influence of contrast agent on LAV% measurement (26). Thus, in contrast to previous reports (11,13), we believe that, in the context of single-time-point measurements, both non-enhanced and contrast-enhanced CT scans can be used for the quantification of CT-based emphysema. Comparable observations have also been made in a previous study noting that the administration of contrast agent did not significantly affect the HU value distribution in the lung parenchyma (27). Similarly, a study by Pauls et al. (28) using contrast-enhanced CT for the quantification of emphysema could demonstrate a significant correlation between emphysema and various lung function parameters, especially the total lung capacity. In another study by Na et al. (12) using contrast-enhanced CT for lung densitometry, the severity of emphysema as quantified from LAV% was more predictive than pulmonary function test for the risk of pulmonary complications after pulmonary lobectomy.

The present study has some limitations. Compared to previous studies, we used an unselected patient cohort, e.g. patients with lung tumors or previous lung resection. This can be considered a potential limitation of this study and might explain the relatively weak correlation between LAV% and TI when compared to previous reports (10,29,30). For example, Fischer et al. (10), who used a prototype of our AI-based software, found very strong correlations between LAV% and TI for two different reconstruction methods ($\varrho = -0.86$; $\varrho = -0.85$) in their study. Thus, it might be important to apply this method only in the assessment of images acquired for non-operated rather than operated patients. The fact that the correlation between LAV% and TI was even higher in the contrast-enhanced group may also be related to the heterogeneity of our patient cohort.

Another important limitation is that based on the hospital's medical records used for our retrospective data analysis, the diagnosis of emphysema was not consistently available. Therefore, it is possible that increased LAV% values may not be or not only be associated with emphysema, albeit we assume that in the majority of our patients it is (Fig. 2). Furthermore, due to the retrospective nature of

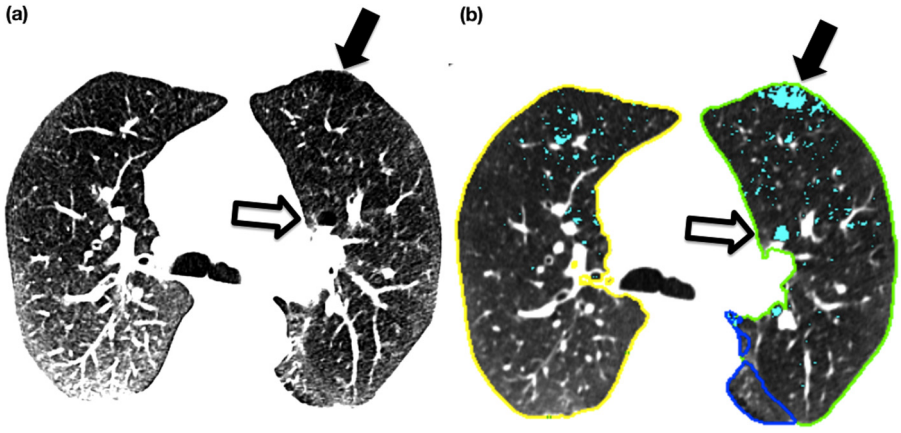

Fig. 2. Axial CT images of a 66-year-old man. (a) Axial CT shows areas of emphysema (bold arrow) as well as paraseptal bullae (open arrow) in correlation with (b) the AI-based color-coded LAV map. The TI in this patient was 57.32% and the LAV% was 13.50. AI, artificial intelligence; CT, computed tomography; LAV%, low attenuation volume percentage; TI, Tiffeneau-Pinelli Index.

the study all image reconstructions were performed according to the institutional clinical standard with a slice thickness of 2.0 mm, which is larger than the Radiological Society of North America (RSNA)/Quantitative Imaging Biomarkers Alliance (QIBA) recommendations (31). For the same reason, a sharp reconstruction kernel (l70) was used, although typically smooth reconstruction algorithms are applied for quantitative CT analysis (32). However, there are studies that suggest that LAV% may be quantified regardless of slice thickness and reconstruction kernel, if these parameters are kept constant (10,33). Another limitation is that the influence of contrast agent on CT based LAV % measurement is evaluated by comparing two different patient groups. As individual factors such as disease-related structural changes in the lung parenchyma and so on might influence LAV% measurement, an intraindividual comparison of exams with and without contrast-enhanced CT would have been favorable. However, the increased radiation associated with this approach would not have been justified. Therefore, our data do not allow us to draw any conclusion regarding the results of longitudinal studies. Furthermore, in the context of an intraindividual approach, other variables potentially affecting lung density would still have to be considered. To assess for the comparability of patients in both study groups, we analyzed both patient groups for any differences that might have influenced spirometry results or CT scans. All but one characteristic was found to be comparable between the two groups apart from the time interval between spirometry and CT acquisition.

In conclusion, our findings suggest that the use of intravenous contrast agent does not influence AI-based LAV% measurement. Although a slight decrease in LAV% was observed in the group of patients with contrast-enhanced CT, the correlation with TI was not significantly different to the patient group with non-enhanced CT.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The third author, Stefan O Schoenberg, has a cooperation with Siemens Healthineers that does not bias the content of the manuscript. The authors confirm that there is no other conflict of interest.

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