Original Article

Quantitative assessment of lung structure changes in low-intensity smokers: a retrospective study in a Chinese male cohort

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Background: With an increasing number of smokers who consume fewer cigarettes, it is crucial to understand the lung structure changes of low-intensity smoking. This study aimed to investigate the lung structure changes in low-intensity smokers in a Chinese male cohort.

Methods: Chest computed tomography (CT) examinations of 465 asymptomatic healthy male participants were divided into non-smoking (n=256), light-smoking (n=84), intermediate-smoking (n=85), and heavy-smoking (n=40) groups. Low-intensity smokers (fewer than 10 cigarettes per day) were included (n=32), and a new group of non-smokers was generated using propensity score matching according to age. Quantitative CT parameters, including the volume of the intrapulmonary vessel (IPVV), the volume of the lung, mean lung density (MLD), the low-attenuation areas below –910 Hounsfield units (LAA-910), and the volume ratio of intrapulmonary vessel to the lung for the total lung and each lobe were measured. Quantitative CT parameters were compared among the four smoking groups and also between the low-intensity smokers and non-smokers. Binary logistic regression was used to determine the independent quantitative CT measurements of smoking intensity.

Results: Compared with that in non-smokers, the IPVV and the MLD of the total lung and five lobes was significantly higher in light smokers ($P<0.05$); meanwhile, the LAA-910 of the total lung and five lobes of the light and intermediate smokers were significantly lower ($P<0.05$). The IPVV of the total lung and five lobes was significantly higher in the low-intensity smoking group ($P<0.05$). The IPVV of the total lung was the independent factor for discriminating between the non-smokers and light smokers (odds ratio =1.040; 95% confidence interval: 1.027–1.053) and between the non-smokers and low-intensity smokers (odds ratio =1.034; 95% confidence interval: 1.013–1.055).

Conclusions: CT-quantified measurements of the IPVVs and MLD increased in light and intermediate smokers. The IPVV of the total lung was selected as the independent factor between non-smokers and light smokers and between non-smokers and low-intensity smokers.

Keywords: Low-intensity smoking; quantitative computed tomography (quantitative CT); mean lung density (MLD); volume of the intrapulmonary vessel (IPVV); emphysema

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Introduction

Conditions attributable to tobacco exposure constitute a rapidly rising global health burden (1,2). Increasing awareness of the harms of cigarette smoking and tobacco control policies have led to decreases in smoking prevalence; however, the percentage of low-intensity smokers (fewer than 10 cigarettes per day) has increased (3). Despite the decline in cigarette smoking, the most common smoking-related pulmonary disease, chronic obstructive pulmonary disease (4,5), has risen in incidence to become the third leading cause of death worldwide (1).

In the past, smoking a few cigarettes was generally believed to be relatively safe. However, Hackshaw *et al.* (6) demonstrated that no safe level of smoking exists, including even one cigarette per day. Evidence from large prospective cohorts indicates that low-intensity smoking is associated with disproportionately high risks of cardiovascular events and a higher risk of various cancers (7-9). Although lung function has been shown to be compromised in low-intensity smokers (10), relatively few studies have examined the lung structure changes in this population. Thus, the lung structure changes of smokers with different smoking intensities, especially low-intensity smokers, remains unknown.

Smoking can lead to impaired endothelial function in healthy individuals, which is an early event of vascular disease. Consequently, reduced blood flow in the small blood vessels may lead to loss of alveolar septa, which can result in emphysema. Therefore, the changes in pulmonary vessels and the growth of emphysema are important in the evaluation of smoking-related lung diseases (11). In our previous study of a Chinese male cohort, we confirmed an expansion of the volume of the pulmonary vessels and an increase in lung density in both current and former smokers (12), which is consistent with other researches (13,14).

To the best of our knowledge, it is unknown how pulmonary vessels, emphysema, and lung density change with the increase in smoking frequency. We hypothesized that even low-intensity tobacco exposure would lead to structural changes in the lung. Thus, this study was conducted to evaluate the quantitative lung structure changes in different-intensity smokers based on non–contrast-enhanced chest computed tomography (CT) images; moreover, the quantitative predictors of the lung structure changes in light- and low-intensity smokers were identified. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-1171/rc).

Methods

Participants

All participants were fully informed of the nature of the study and provided written informed consent for participation. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), approved by the Ethics Committee of the Institutional Review Board of Xi'an Jiaotong University (No. 2013-114-1), and is registered online (http://www.chictr.org/en/; registration No. ChiCTR-OCH-14004934).

Chest CT images were retrospectively collected from August 2017 to August 2018 from an annual lung nodule screening cohort.

The inclusion criteria were as follows: (I) males who underwent a non-contrast chest CT scan for the lung nodule screening; (II) a complete history of smoking, including years of smoking, smoking intensity, and onset age of smoking; and (III) age between 18 and 80 years. Meanwhile, the exclusion criteria were as follows: (I) a congenital deformity of the spine or thorax (n=5); (II) a history of lobectomy or pneumonectomy (n=10); (III) noticeable respiratory or motion artifacts (n=18); (IV) lesions apparent in the CT scan, such as the diffused emphysema, lobar consolidation, nodules or mass of the lung, active tuberculosis or tuberculosis involving multiple pulmonary lobes, lung atelectasis, interstitial lung diseases or pleura effusion (n=55); and (V) severe heart, liver, or kidney dysfunction (n=2).

Smokers were divided into light- (0–19.9 pack-years), intermediate- (20–39.9 pack-years), and heavy-smoking groups (more than 40 pack-years) according to the amount of smoke exposure quantified by pack-years (15). *Figure 1* shows a flowchart detailing how participants were selected. Low-intensity smokers were considered those who consume fewer than 10 cigarettes per day regardless of the total smoking index quantified by pack-years (3).

Imaging technique

CT scans were performed using a Gemini 64-multislice positron emission tomography/CT (PET/CT) scanner (Philips Healthcare, Best, the Netherlands) from the apex to the base of the lungs at the end-inspiratory phase. All the examinations were performed without enhancement,

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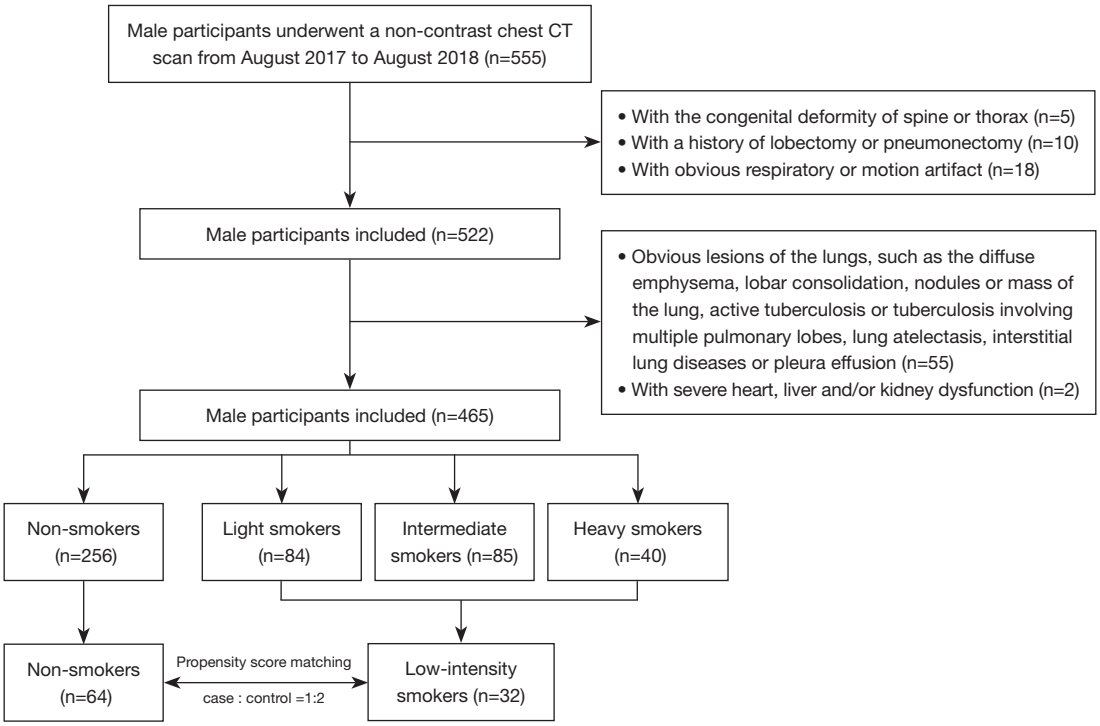

Figure 1 Study selection and design. CT, computed tomography.

with an automatic current at a range of 100–300 mAs (based on body weight) and a kilovoltage of 120. Other scanning parameters were held constant (helical acquisition; gantry rotation time, 0.5 seconds; reconstructed section thickness, 1.25 mm; reconstructed section interval, 1.25 mm; 512 × 512 reconstruction matrix). All data were reconstructed using the full iterative reconstruction.

Quantitative assessment of the lung volume, intrapulmonary vessels, and the emphysema

Lung tissue segmentation was performed at the First Affiliated Hospital of Xi'an Jiaotong University on a lung workstation (Dexin, Xi'an, China). Five pulmonary lobes, including the right upper lobe (RUL), right middle lobe (RML), right lower lobe (RLL), left upper lobe (LUL), and left lower lobe (LLL) were segmented (16-18). A computational geometric method was employed to segment the intrapulmonary vessels, as previously described (12).

Measurements of the volume of the lung (LV) (mL), volume of the intrapulmonary vessels (IPVV) (mL), and the ratio of the IPVV to LV (IPVV/LV) for the total lung and individual lobes were estimated (*Figure 2*). Emphysema was quantified using the percentage of low attenuation areas below –910 Hounsfield units (HU) (LAA-910) (*Figure 3*). The mean density of each lung voxel was averaged as the mean lung density (MLD) (HU). Two experienced radiologists (R.S. and C.S.) with >10 years of experience in thoracic image interpretation reviewed the CT images. The segmentation results could be subjected to manual correction when the results were not satisfactory. Two cases with interstitial lung diseases were corrected manually in the bilateral lower lobes, with no more than a 1% decrease in the pulmonary vessel volume.

Statistical analysis

SPSS 25 (IBM Corp., Armonk, NY, USA) was used for the statistical analyses. Patients' baseline characteristics and the quantitative CT parameters are summarized according to smoking status as the mean and standard deviation for normally distributed variables and as the median and interquartile range for skewed variables.

A one-way analysis of variance was used to assess the differences between the groups for normally distributed variables, and the Kruskal-Wallis test was used for those without normally distributed variables. Subsequently, multiple comparisons between the two groups were

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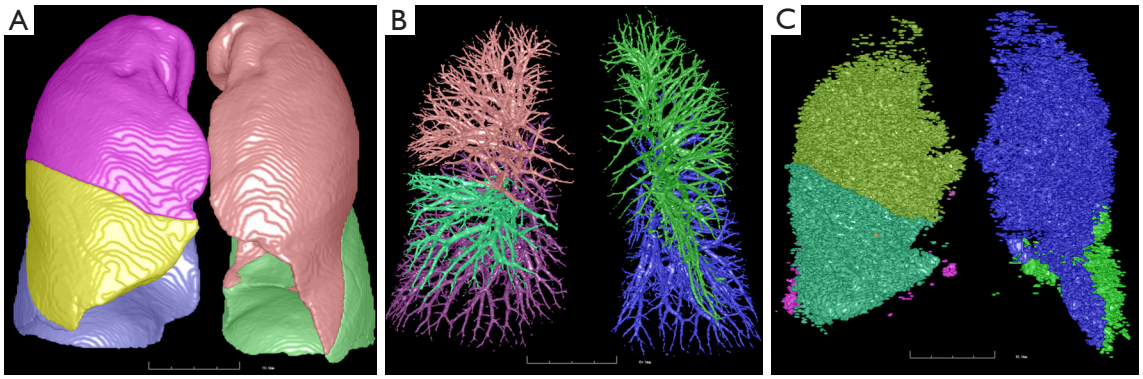

Figure 2 Segmentation of the five lung lobes, intrapulmonary vessels, and emphysema. A 59-year-old, non-smoking, male. The five lung lobes (A), intrapulmonary vessels (B), and emphysema (C) were segmented.

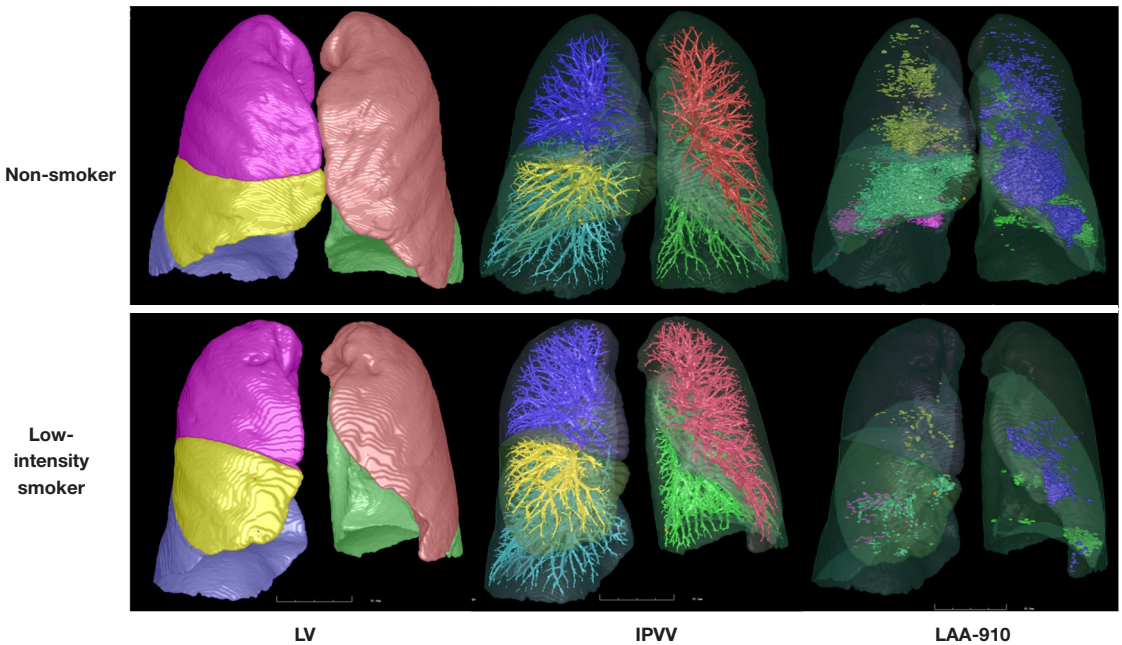

Figure 3 Visual examples of the image-based metrics. The top panels show the segmentation results from a non-smoking participant, and the bottom panels show the segmentation results from a low-intensity smoking participant. In the images, intrapulmonary vessels appear more abundant in the low-intensity smokers than in the non-smokers, while the emphysema, reflected by LAA-910, appears minor. IPVV, intrapulmonary vessel volume; LV, lung volume; LAA-910, low attenuation area below –910 Hounsfield units.

conducted using the least significant difference for the equal variance or the Tamhane T2 test for the unequal variance. To compare the non-smokers and low-intensity smokers, a new control group of non-smokers was generated using propensity score matching according to age. The ratio of the case to control was 1:2.

Study-specific odds ratios and 95% confidence intervals for smoking intensity were estimated using binary logistic regression with non-smokers being used as the referent group. For all statistical analyses, a P value <0.05 was

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considered significant.

Results

Comparisons between non-smokers, light smokers, intermediate smokers, and heavy smokers

Clinical characteristics

A total of 465 males were included in the analysis, and their detailed basic information is shown in *Table 1*. There were 256 non-smokers, 84 light smokers, 85 intermediate smokers, and 40 heavy smokers. The heavy-smoking groups was significantly older than were the other three groups (P<0.05).

Quantitative assessment of the lung structures

LVs increased as smoking intensity increased. The LV of total lung and bilateral upper lobes for heavy smokers was significantly elevated compared with that in non-smokers (P<0.05). Moreover, the LVs in the light and intermediate smokers were non-significantly higher than that of non-smokers (P>0.05; *Table 1*).

The IPVV of smokers was higher than that of non-smokers, while the IPVV decreased as the smoking index increased (see Table S1 for the correlation coefficients between the quantitative parameters and the smoking index in all three smoking groups). The IPVV and IPVV/LV of the total lung and five lobes were significantly higher in the light and intermediate smokers than in the non-smokers (P<0.05), and the IPVV of the total lung and bilateral lower lobes in heavy smokers were significantly higher than those of the non-smokers (P<0.05). Compared with light smokers, heavy smokers had a significantly lower IPVV of the total lung, RML, and LUL (P<0.05) and IPVV/LV of the bilateral upper (P<0.05; *Table 1*).

The LAA-910 of smokers was lower than that of non-smokers, and the LAA-910 increased with the increase in smoking intensity. The LAA-910 for the total lung and five lobes of light and intermediate smokers was significantly lower than that of non-smokers (P<0.05) and that of the

Table 1 Basic demographic characteristics of the patients

Characteristic	Non-smoking (n=256)	Light smoking (n=84)	Intermediate smoking (n=85)	Heavy smoking (n=40)	F	P
Age (years)	60.00 (53.00 to 66.75)	57.62±13.16	57.43±8.45	62.00 (60.00 to 65.75)†‡	11.781[a]	0.008
Height (cm)	172.00 (170.00 to 175.00)	173.50±5.39	172.00 (170.00 to 174.50)	172.00 (170.00 to 175.00)	4.945[a]	0.176
Weight (kg)	72.66±8.85	75.36±10.96*	73.61±9.18	74.02±9.43	1.426	0.234
Body mass index (kg/m^2)	24.44±2.51	24.98±3.11	24.80±2.66	24.85±2.93	0.811	0.488
Pack (per day)	NA	1 (0.6 to 1)	2 (2 to 2)†	2 (2 to 3.87)†‡	121.246[a]	<0.001
Duration (years)	NA	20 (15 to 30)	30 (20 to 30)†	40 (31.5 to 40)†‡	51.558[a]	<0.001
Smoking index (pack-years)	NA	20 (6 to 15)	30 (20 to 30)†	40 (40 to 58.13)†‡	181.480[a]	<0.001
Onset age of smoking (years)	NA	33.00 (26.25 to 40.75)	29.00 (22.00 to 33.00)†	23.00 (20.00 to 29.75)†‡	27.480[a]	<0.001
With ILD (cases)	0	0	0	2		
LV (mL)						
TL	5,134.81±721.54	5,205.32±768.04	5,273.57±702.33	5,434.11±830.39*	0.575	0.632
RUL	1,059.41±176.07	1,061.23±188.75	1,091.24±186.75	1,136.62±170.09*†	0.390	0.760
RML	502.12±103.59	532.47±98.87*	503.08±120.27	512.22±122.88	2.014	0.111
RLL	1,209.95±243.64	1,193.17±274.15	1,231.04±233.39	1,272.51±258.28	0.758	0.518
LUL	1,291.06±190.58	1,327.09±192.34	1,322.60±176.28	1,360.51±204.96*	0.246	0.864
LLL	1,072.28±248.41	1,091.37±253.58	1,125.61±226.74	1,152.24±273.27	0.469	0.704

Table 1 (*continued*)

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Table 1 (*continued*)

Characteristic	Non-smoking (n=256)	Light smoking (n=84)	Intermediate smoking (n=85)	Heavy smoking (n=40)	F	P
IPVV (mL)						
TL	118.83±23.23	138.75±20.82*	135.39±20.03*	129.55±15.56*†	24.581	<0.001
RUL	22.53±5.71	25.67±4.97*	24.91±5.07*	24.30±3.42	9.580	<0.001
RML	9.56±2.53	11.48±2.66*	10.89±3.07*	10.18±2.51†	13.609	<0.001
RLL	31.64±7.00	37.00±6.75*	36.84±6.03*	35.09±5.04*	21.539	<0.001
LUL	26.48±5.65	30.32±5.28*	29.11±5.24*	28.08±3.97†	13.059	<0.001
LLL	28.62±6.89	34.27±6.67*	33.65±6.08*	31.89±5.72*	22.631	<0.001
IPVV/LV (%)						
TL	2.30 (1.92 to 2.69)	2.58 (2.29 to 3.05)*	2.50 (2.25 to 2.88)*	2.44±0.48	32.257[a]	<0.001
RUL	2.08 (1.78 to 2.50)	2.45±0.44*	2.31±0.45*	2.17±0.39†	27.826[a]	<0.001
RML	1.94±0.50	2.17±0.39*	2.18±0.41*	2.02±0.39	8.806	<0.001
RLL	2.57 (2.14 to 3.12)	3.13 (2.49 to 3.62)*	2.87 (2.54 to 3.51)*	2.70 (2.42 to 3.38)	35.234[a]	<0.001
LUL	2.08±0.50	2.32±0.45*	2.23±0.44*	2.11±0.41†	6.117	<0.001
LLL	2.67 (2.15 to 3.25)	3.08 (2.56 to 3.60)*	2.91 (2.53 to 3.47)*	2.88±0.73	27.402[a]	<0.001
LAA-910 (mL)						
TL	672.53 (279.92 to 1,025.41)	392.94 (180.93 to 801.96)*	394.24 (139.41 to 820.02)*	540.80 (320.41 to 1,032.68)	17.002[a]	<0.001
RUL	140.13 (47.37 to 222.99)	80.29 (31.5 to 168.72)*	65.50 (26.51 to 192.77)*	155.13±128.40	14.431[a]	0.002
RML	130.10 (64.05 to 193.06)	74.92 (42.63 to 132.96)*	70.79 (27.53 to 135.43)*	119.79±89.64	30.157[a]	<0.001
RLL	73.48 (19.11 to 158.82)	33.99 (10.45 to 98.85)*	36.35 (11.7 to 116.69)*	57.97 (18.1 to 142.36)	15.910[a]	0.001
LUL	225.47 (104.04 to 357.82)	164.98 (74.51 to 275.81)*	143.00 (50.24 to 304.70)*	192.40 (120.17 to 387.88)	13.992[a]	0.003
LLL	54.58 (17.83 to 148.33)	34.54 (10.51 to 87.50)*	46.31 (13.26 to 103.52)	55.30 (22.75 to 139.04)	8.809[a]	0.032
MLD (HU)						
TL	−834.92 (−846.25 to −814.31)	−820.54±21.95*	−824.46 (−839.13 to −806.54)*	−830.84±18.57	17.017[a]	0.001
RUL	−842.06 (−851.86 to −825.74)	−834.84 (−845.35 to −817.14)*	−833.65±19.56	−839.95±16.66	13.499[a]	0.004
RML	−856.11 (−863.96 to −840.55)	−843.62±16.20*	−842.6±17.97*	−850.62±16.35	25.923[a]	<0.001
RLL	−819.27 (−835.59 to −792.79)	−801.75 (−827.03 to −780.21)*	−809.11 (−828.02 to −786.76)	−813.42±25.51	15.290[a]	0.002
LUL	−843.31 (−856.05 to −829.19)	−841.15 (−850.76 to −824.58)	−836.07±20.03	−843.32±17.64	9.713[a]	0.021
LLL	−812.63 (−832.74 to −784.47)	−800.84 (−822.37 to −774.93)*	−810.92 (−823.68 to −782.29)	−810.53±27.65	8.017[a]	0.046

Data are presented as the mean ± standard deviation or as the median (interquartile range). *, significantly different from non-smokers (P<0.05); †, significantly different from light smokers (P<0.05); ‡, significantly different from intermediate smokers (P<0.05); [a], independent Kruskal-Wallis test. IPVV, intrapulmonary vessel volume; LV, lung volume; MLD, mean lung density; LAA-910, low attenuation area below −910 Hounsfield units; TL, total lung; RUL, right upper lobe; RML, right middle; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; NA, not applicable.

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Table 2 Binary logistic regression models for different intensities of smoking

Subgroup analysis	Characteristic	b	Standard error	P	Odds ratio	95% confidence interval	
						Upper limit	Lower limit
Non-smokers *vs.* light smokers	$IPVV_{TL}$	0.039	0.006	<0.001	1.040	1.027	1.053
Non-smokers *vs.* intermediate smokers	$IPVV_{RLL}$	0.180	0.034	<0.001	1.197	1.120	1.279
	$IPVV/LV_{TL}$	–5.080	1.123	<0.001	0.006	0.001	0.056
	$IPVV/LV_{LLL}$	3.380	0.765	<0.001	29.365	6.558	131.493
	MLD_{RML}	0.091	0.018	<0.001	1.096	1.057	1.135
	MLD_{RLL}	0.051	0.014	<0.001	1.052	1.024	1.081
	MLD_{LLL}	–0.099	0.019	<0.001	0.906	0.873	0.940
Non-smokers *vs.* heavy smokers	$IPVV_{RUL}$	0.099	0.050	0.050	1.104	1.000	1.219
	$IPVV_{RLL}$	0.116	0.036	0.001	1.123	1.046	1.205
	$IPVV/LV_{RUL}$	–1.727	0.625	0.006	0.178	0.052	0.605
Light smokers *vs.* intermediate smokers	$IPVV/LV_{RUL}$	–1.880	0.575	0.001	0.153	0.049	0.471
	MLD_{RML}	0.060	0.018	0.001	1.062	1.025	1.100
	$LAA\text{-}910_{LLL}$	0.008	0.003	0.018	1.008	1.001	1.014
Light smokers *vs.* heavy smokers	$IPVV/LV_{RUL}$	–1.660	0.536	0.002	0.190	0.067	0.543
Intermediate smokers *vs.* heavy smokers	MLD_{RML}	–0.024	0.011	0.039	0.977	0.955	0.999

IPVV, intrapulmonary vessel volume; MLD, mean lung density; LAA-910, low attenuation area below –910 Hounsfield units; TL, total lung; LV, lung volume; RUL, right upper lobe; RML, right middle; RLL, right lower lobe; LLL, left lower lobe.

LLL in intermediate smokers (*Table 1*).

Compared with that in non-smokers, the MLD of the total lung and five lobes was significantly higher in light smokers (P<0.05; *Table 1*).

Binary logistic regression analysis

Table 2 shows logistic regression analyses of the independent biomarkers for different smoking intensities. The IPVV of the total lung (odds ratio =1.040; 95% confidence interval: 1.027–1.053) was the independent factor for discriminating between the non-smokers and light smokers.

Comparisons between non-smokers and low-intensity smokers

There were 32 participants were included in the low-intensity smoking group and 64 in the control group. The age, height, weight, and body mass index were not significantly different between the two groups (*Table 3*). Compared with that in non-smokers, the IPVV of the total lung and five lobes was significantly increased (P<0.05), as was the LV of the total lung, RML, and LUL (P<0.05). The IPVV/LV was not significantly different between the two groups (P>0.05).

In the logistic regression analysis, the IPVV of the total lung (odds ratio =1.034; 95% confidence interval: 1.013–1.055) and the LV of the LUL (odds ratio =1.003; 95% confidence interval: 1.000–1.005) were the independent factors for discriminating between the non-smokers and low-intensity smokers.

Discussion

Despite a growing body of evidence pointing to the association between low-intensity smoking and a higher risk of various cancers (7-9), the structure changes of the lung parenchyma and pulmonary vasculature in low-intensity smokers remain unclear. In this single-center, retrospective study, the effects of low-intensity exposure to cigarette smoke on lung structure were quantitatively assessed *in vivo*, which gleaned valuable insights.

In our study, the LV continued to increase with the

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Table 3 Comparisons between non-smokers and low-intensity smokers

Quantitative parameter	Non-smoking (n=64)	Low-intensity smoking (n=32)	t/Z	P
Age (years)	68.50 (56.25 to 73.00)	68.50 (56.50 to 73.75)	0.412	0.680
Height (cm)	171.63±4.17	172.50±5.48	0.870	0.387
Weight (kg)	71.75±8.63	71.97±8.84	0.118	0.906
Body mass index (kg/m^2)	24.34±2.60	24.14±2.15	0.373	0.710
Cigarette (days)	NA	5.00 (4.12 to 6.00)	NA	NA
Duration (years)	NA	28.50 (20.00 to 40.00)	NA	NA
Age of smoking onset (years)	NA	36.50±12.30	NA	NA
LV (mL)				
TL	4,957.73±782.90	5,340.05±749.68	2.287	0.024
RUL	1,047.70±174.11	1,094.23±223.44	1.120	0.265
RML	486.29±94.81	532.29±115.53	2.081	0.040
RLL	1,147.95±237.80	1,225.39±260.28	1.457	0.158
LUL	1,255.46±232.76	1,388.39±184.19	2.817	0.006
LLL	1,020.32±243.49	1,099.76±266.95	1.459	0.148
IPVV (mL)				
TL	116.23±23.28	133.13±20.64	3.480	0.001
RUL	22.80±5.87	25.30±5.25	2.037	0.044
RML	9.36±2.40	11.05±2.72	3.107	0.003
RLL	30.18±6.36	34.87±6.85	3.318	0.001
LUL	26.24±5.94	26.48 (22.13 to 30.33)	3.051	0.002
LLL	27.64±6.93	31.80±7.07	2.754	0.007
IPVV/LV (%)				
TL	2.32 (1.88 to 2.90)	2.40 (2.14 to 2.92)	1.294	0.196
RUL	2.15 (1.76 to 2.66)	2.35±0.44	1.426	0.154
RML	1.98±0.57	2.10±0.36	1.226	0.223
RLL	2.76±0.86	2.68 (2.43 to 3.33)	1.317	0.188
LUL	2.02 (1.74 to 2.60)	2.05 (1.85 to 2.53)	0.968	0.333
LLL	2.87±0.99	2.98±0.75	0.614	0.541
LAA-910 (mL)				
TL	623.76 (148.68 to 1,099.86)	632.01±414.34	0.047	0.963
RUL	117.23 (22.98 to 219.19)	132.96±107.32	0.113	0.910
RML	112.86 (38.15 to 192.95)	78.86 (49.48 to 160.06)	0.497	0.619
RLL	63.32 (11.70 to 158.90)	86.83±69.84	0.330	0.741
LUL	204.45 (53.55 to 354.25)	229.00±151.31	0.408	0.683
LLL	41.38 (10.18 to 158.97)	49.56 (19.31 to 116.74)	0.070	0.944

Table 3 (*continued*)

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Table 3 (*continued*)

Quantitative parameter	Non-smoking (n=64)	Low-intensity smoking (n=32)	t/Z	P
MLD (HU)				
TL	−834.93 (−846.09 to −808.13)	−830.49 (−843.48 to −813.50)	0.101	0.920
RUL	−840.39 (−851.64 to −818.42)	−835.24±16.64	0.389	0.698
RML	−850.16 (−864.06 to −831.16)	−847.75±15.13	0.229	0.819
RLL	−817.01 (−832.16 to −787.04)	−816.31 (−831.18 to −799.51)	0.105	0.916
LUL	−837.46±23.52	−841.2±16.52	0.192	0.848
LLL	−800.57±38.07	−813.96 (−826.49 to −787.34)	0.175	0.861

Data are presented as mean ± standard deviation or median (interquartile range). IPVV, intrapulmonary vessel volume; LV, lung volume; MLD, mean lung density; LAA, low attenuation area; TL, total lung; RUL, right upper lobe; RML, right middle; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; NA, not applicable.

increasing intensity of smoking, with the LV being significantly higher in heavy smokers than in non-smokers for the total lung and bilateral upper lobes. The IPVV and MLD were higher in light and intermediate smokers than in non-smokers, with the IPVV and MLD decreasing as smoking intensity increased. In contrast, the LAA-910, an indicator of emphysema, was lower in intermediate smokers than in non-smokers and increased as smoking intensity increased. Second, the IPVV of the total lung and five lobes was significantly higher in low-intensity smokers than in non-smokers. Third, the IPVV of the total lung was selected as the independent factor for discriminating between non-smokers and light smokers and between non-smokers and low-intensity smokers.

Studies in animal models have shown that cigarette smoke exerts a direct effect on pulmonary vascular structure, resulting in medial hypertrophy of the vessel wall, impairment of vasoconstriction and vasodilation responses, and vascular lumen narrowing, all of which contribute to the development of pulmonary hypertension (13,14,19,20). In our previous study, the IPVV was higher in light-to-moderate smokers, which showed that nicotine-induced pathological angiogenesis, as the pulmonary inflammatory response to cigarette smoke (20), can be measured by the IPVV on non-contrast CT images. Conversely, cigarette smoke increases the proliferative potential of nonexposed cells through the secretion of inflammatory molecules (21). Additionally, the alveolar collapse due to the decreased lung surfactant in the surrounding lung parenchyma of pulmonary vessels may also contribute to the enlargement of the IPVV in lower-intensity smokers and in light or intermediate smokers (22). In several human studies, cigarette exposure was also associated with higher pulmonary blood vessel volumes in the Multi-Ethnic Study of Atherosclerosis cohort (13) and Framingham Heart cohort (14). Ritchie *et al.* (23) also reported a higher ratio of tiny blood vessel volume to total pulmonary vessel volume in young or low-intensity smokers, and Sun *et al.* (24) found the IPVV of smokers to be increased.

Pulmonary emphysema is characterized by the abnormal, permanent enlargement of air spaces distal to the terminal bronchioles, accompanied by the destruction of the walls. Changes in lung density are key characteristics of lung emphysema, pneumonia, and pulmonary fibrosis. In this study, smokers had an increased MLD and LAA-910 as compared to non-smokers. One hypothesis to explain this phenomenon holds that inflammation due to cigarette smoke exposure may effectively mask emphysema by increasing local lung tissue density. Ritchie *et al.* (23) also reported a higher frequency of ground-glass opacification in young smokers or low-intensity smokers. Additionally, smoking has been found to be a trigger of inflammation and parenchymal destruction that is mediated by toll-like receptor 3 (25).

The qualitative assessment of the lung structures has mainly focused on individuals with chronic obstructive pulmonary disease (26,27) or heavy smokers in whom chronic obstructive pulmonary disease has not yet developed (28)]. The participants in our study were smokers at the early stage without the development of chronic obstructive pulmonary disease. Ritchie *et al.* (23) also showed that even a relatively short period of regular tobacco smoking results in identifiable lung abnormalities before smokers typically receive diagnoses of chronic obstructive pulmonary disease.

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According to computer-aided quantitative measurement of pulmonary parenchyma, IPVV was selected as a sensitive biomarker for evaluating lung structure changes in light and low-intensity smokers. Pistenmaa *et al.* (29) indicated that pulmonary vascular differences might be relevant in disease progression in a chronic obstructive pulmonary disease cohort. Our study provides evidence that smoker-related angiogenesis can be detected earlier than can emphysema due to the pulmonary inflammation response to cigarette smoke in the early stage.

Certain limitations to this study should be mentioned. First, as we employed a retrospective design, the recall bias of the smoking history was unavoidable, especially for the patients included in the intermediate and heavy smoking group because they began smoking at a younger age. The second limitation is the small size of the sample, and our findings remain to be validated in a larger cohort. Moreover, only male participants were included in our study; thus, the effects of low-intensity smoking on the lungs also needed to be quantified in female participants. Third, whether the expansion of the IPVV in light smokers or low-intensity smokers is associated with impaired lung function or pulmonary hypertension remains unclear. Therefore, a longitudinal cohort study with a pulmonary function test should be conducted. The fourth limitation is the inevitable age imbalance between heavy smokers and other groups. The older age in heavy smokers might have led to larger lung volume, a higher proportion of emphysema, and decreased lung vessel volume.

Conclusions

The IPVVs and MLDs were higher in light and intermediate smokers and decreased as the smoking index increased. In contrast, the LAA-910, an index of emphysema, was lower in light and intermediate smokers and increased as smoking index increased. The IPVV of the total lung was selected as the independent factor in discriminating between non-smokers and light smokers and between non-smokers and low-intensity smokers. Our data support the presence of early lung structure abnormalities in smokers, which suggests that even a relatively short period of regular tobacco smoking results in discernable lung abnormalities.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-24-1171/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-1171/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All participants were fully informed of the nature of the study and provided written informed consent for participation. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of the Institutional Review Board of Xi'an Jiaotong University (No. 2013-114-1).

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