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Research Article

How are Lung Volume and Respiratory Muscles Affected in Non-Severe Patients With Covid-19?

Akciğer Hacmi ve Solunum Kasları Ağır Seyretmeyen Covid-19 Hastalarında Nasıl Etkilenir?

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Abstract

Aim: Coronavirus-2019 (Covid-19) primarily affects the respiratory system, and how it affects respiratory muscles and lung volume is still not fully understood. Our study aimed to assess the time-dependent changes that may occur in lungs and respiratory muscle sizes on chest computed tomography (CT) in adult coronavirus disease 2019 (COVID-19) patients.

Material and Methods: The clinical and radiological records of 101 adult patients who had at least two non-contrast chest CT images in stage 1 (0-4 days) and stage 6 (>28 days) were collected retrospectively. ImFusion Suite program were used to calculate lung volumes, and the cross-sectional areas of the pectoral and intercostal muscles were also calculated using with "ImageJ" program.

Results: One-hundred one patients (51 females, 50.49%) were included in the study. ANCOVA revealed a significant stage*side interaction effect regarding cross-sectional area (CSA) of intercostal muscles [(p=.010; η^2p=.064)]. There was no significant difference between the two stages in terms of CSA of pectoralis major and minor muscles [(p=.314; η2p=.010), (p=.644; η^2p=.002)] respectively and lung volume [(p=.340; η^2p=.009)].

Conclusion: Covid-19 pneumonia causes an atrophy in respiratory muscles. However, it seems to have a nonsignificant effect on auxiliary respiratory muscles and lung volume. Further investigation of respiratory muscles and respiratory muscle training to reduce the risk of serious complications during viral infections are required.

Keywords: Covid-19, computed tomography, imaging, lung volume, respiratory muscles

Öz

Amaç: Coronavirus-2019 (Covid-19) öncelikle solunum sistemini etkiler ve solunum kaslarını ve akciğer hacmini nasıl etkilediği hala tam olarak anlaşılamamıştır. Çalışmamız erişkin koronavirüs hastalığı 2019 (COVID-19) hastalarında akciğer bilgisayarlı tomografisinde (BT) akciğerlerde ve solunum kası boyutlarında zamana bağlı olarak oluşabilecek değişiklikleri değerlendirmeyi amaçladı.

Materyal ve Metot: Evre 1 (0-4 gün) ve evre 6'da (>28 gün) en az iki kontrastsız göğüs BT görüntüsü olan 101 erişkin hastanın klinik ve radyolojik kayıtları geriye dönük olarak toplandı. Akciğer hacimlerini hesaplamak için ImFusion Suite programı kullanıldı ve pektoral ve interkostal kasların kesit alanları da "ImageJ" programı kullanılarak hesaplandı.

Bulgular: Yüz bir hasta (51 kadın, %50,49) çalışmaya dahil edildi. ANCOVA, interkostal kasların kesit alanına (KA) ilişkin önemli bir evre*yan etkileşim etkisi ortaya çıkardı [(p=.010; η^2p=.064)]. Sırasıyla pektoralis major ve minor kaslarının KA'sında [(p=.314; η^2p=.010), (p=.644; η^2p=.002)] ve akciğer hacminde [(p=.340; η^2p=.009)] iki evre arasında anlamlı bir fark bulunmadı.

Sonuç: Covid-19 pnömonisi solunum kaslarında atrofiye neden olur. Ancak yardımcı solunum kasları ve akciğer hacmi üzerinde önemsiz bir etkiye sahip olduğu görülmektedir. Viral enfeksiyonlar sırasında ciddi komplikasyon riskini azaltmak için solunum kaslarının daha fazla araştırılması ve solunum kas eğitimi gereklidir.

Anahtar Kelimeler: Covid-19, bilgisayarlı tomografi, görüntüleme, akciğer hacmi, solunum kasları

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INTRODUCTION

The world has been struggling with coronavirus 2019 (Covid-19), which appeared in Wuhan, and spread rapidly causing a pandemic (1). Due to the risk of rapid contagion, early diagnosis, isolation, and early treatment interventions are of great importance in these patients. The Real-Time Polymerase Chain Reaction (RT-PCR) test is used to considered the gold standard for diagnosis; however, the drawbacks of the test include false-negative results especially in the early period of the disease, the time-consuming nature of the test, and the unavailability of the test facilities in some places (2). Thus, radiological methods in identifying the characteristic findings of Covid-19-induced pneumonia are important for early diagnosis and follow-up of the patient's prognosis (3,4). Considering the adverse impact of the Covid-19 infection on the lungs, chest radiology and computer tomography (CT) are extensively used to verify lung involvement (5).

Thin-section CT is an important tool in the early detection, monitoring, and evaluating the efficiency of the treatments. At the onset of the disease, the sensitivity of the RT-PCR test and chest CT are 71% and 98%, respectively; indicating the reliability of using CT primarily in symptomatic cases with suspicious chest X-ray who are prone to develop complications (3). Some studies in the relevant literature have reported that the normal lung volume may decrease due to alveolar collapse in patients with Covid-19 pneumonia (6). Additionally, the proinflammatory effects of Covid-19 and the deconditioning during the convalescent period may lead to losses in both muscle strength and endurance (7). However, long-term follow-up studies and objective data on the subject are scarce (8).

Previously published studies have evaluated the typical and atypical CT degree of Covid-19 pneumonia (9), the time-dependent variation of CT findings (10), and the correlation between CT features and clinical characteristics (11). However, to the best of our knowledge, there are no studies investigating the time-dependent changes in lung volume and respiratory muscle sizes in Covid-19 patients, and respiratory muscle performance and lung volume are important in developing early rehabilitation strategies. For these reasons, our study aimed to determine the possible time-dependent changes that may occur in lungs and respiratory muscle sizes on the CT images of patients which diagnosed with Covid-19.

MATERIAL AND METHOD

Study plan and study population

Ethical approval for this study was obtained from the Ankara Medipol University Medical Faculty Clinical Research Ethics Committee (Registration date/no: Registration date/no: 23.09.2021/35). This retrospective study imposed no risk for the participants and informed consent was waived. Our cohort composed of 101 patients subjected to the RT-PCR test for suspicious Covid-19 infection between March 30, 2020, and June 30, 2021. To collect data, the clinical and radiological records of 101 adult non-severe Covid-19 patients retrospectively reviewed who: 1. had at least two non-contrast chest CT images in stage 1 (0-4 days) and stage 6 (28 days) (12), 2. had a positive RT-PCR test result at stage 1, and 3. had confirmed CT findings typical to Covid-19 pneumonia detected by a 20 years of experience radiologist. The severe of the COVID-19 score was determined as; development of respiratory rate more than 30 per minute, arterial partial pressure of oxygen ($PaO2$) / oxygen concentration ($FiO2$) of 300 mmHg or less, the rate of resting oxygen saturation was 93% or less, or needed mechanical ventilation (13).

Exclusion criteria were as following: 1. being younger than 18 years of age, 2. being presenting with severe COVID-19 or having a history of intubating (atrophy of the respiratory muscles is the expected finding in mechanically ventilated patients). 3. having a myasthenia gravis or similar muscle disease, 4. having distorted CT images due to major motion artifact, and 5. absence of pectoral and intercostal muscles on CT images. Lung volume (LV in cm^3) and respiratory muscles' cross-sectional areas (CSA in cm^2) were calculated on the CT images in stage 1 and stage 6.

CT protocol

CT imaging carried out using with a single inspiratory phase in a multi-detector CT scanner (Philips Ingenuity Core 128, Philips, Netherlands). Participants were instructed on breath-holding to minimize of the motion artifacts, and CT images were obtained during a single breath-hold. The mean CTDI vol was 8.4±2.0 mGy (range: 5.2-12.6 mGy). The tube voltage was 120kVp with automatic tube and from the raw data. CT images which thickness of 1.5 mm were reconstructed with a matrix size of 512×512 as axial images. No intravenous contrast medium was administered to any patient.

Measuring lung volume

We used the ImFusion Suite program to calculate lung volumes. First, the original CT images that in Digital Imaging and Communications in Medicine (DICOM) format were converted to SPM8 (3D Niftii) format using the "dcm2niigui" software. These images were then used to calculate lung volume in the ImFusion Suite program.

The steps can be summarized as following

1. "Interactive Segmentation" section was activated by selecting "Segmentation" under "Algorithms" tab in ImFusion Suite program.
2. For each image, the borders of the lungs were adjusted in the axial, coronal, and sagittal planes. These borders were painted in all 3 planes by selecting the "Paint Object" tab, to obtain a 3D representation of each lung.
3. By choosing the "Paint Background" tab, the background noise was eliminated.
4. Using the "Accept Segmentation", "Run Segmentation",

"Export as Label Map" and "Export as Annotation" tabs respectively, we completed the 3D model process.

5. Using the 3D models, the lung volumes were obtained via clicking on the "Show Segmentation Statistics" tab, then "Background" and then the "Object" tab. The whole process was repeated for the CT images of both stage 1 and 6 of each participant. The collected lung volumes (in mm^3) were converted to cm^3 and recorded.

Measuring cross-sectional areas of respiratory muscles

The measurement of the cross-sectional areas of the pectoral and intercostal muscles at the determined reference points was performed by two anatomists and a radiologist without access to clinical or laboratory findings. The mean of these three values was recorded in cm^2 for each muscle.

Cross-sectional area of the pectoral muscles

Pectoral muscles were chosen as auxiliary respiratory muscles. To calculate the cross-sectional surface area, all images saved in JPEG format were imported to the "ImageJ" program, that can be obtained free of charge from the https://imagej.nih.gov/ij/download.html. The images were created by selecting "stack image to stack" tab under the "image" tab. In the RadiAnt program, using with the "measurement and tools" tab, one of the lengths of any structure selected location on the image and measured. Then, the measured location was selected in the same section and the image was calibrated using "Set Calibrate" located under the "Analyze" tab. Then, the pectoralis major (PMa) and pectoralis minor (PMi) muscles were determined manually with the reference point of the supraaortic arteries level using the "Free Hand" button of the ImageJ program (Figure 1). The cross-sectional surface areas of the muscles were calculated on an ImageJ tab using the "M" button. The entire process was repeated on both stage 1 and stage 6 of the CT image of each participant and the results were recorded in cm^2.

Cross-sectional area of the intercostal muscles

The intercostal muscles (ICM) were chosen as the main respiratory muscles. To calculate the cross-sectional surface areas, CT images -in DICOM format- were imported to the Imfusion Suite (demo version 2.15.1) program to get a 3D view on axial, sagittal, and coronal planes. These 3D images were used to create screenshots of the sections corresponding to the right and left midclavicular line on the sagittal axis. These screenshots -saved in the Joint Photographic Experts Group (JPEG) format- were imported to the ImageJ program. Using the "straight" button in the ImageJ program, the scale bar on the image was marked and the image was calibrated using with "Set Calibrate" under the "Analyze" tab. Then, in the ImageJ program, the borders of 1, -5 ICMs were identified with manually using the "Free Hand" button. Finally, the cross-sectional surface areas of the muscles were calculated on an ImageJ tab using the "M" key (Figure 2). This process was repeated on both stage 1 and stage 6 of the CT image of each participant and the results were recorded in cm^2.

Statistical analysis

We used Statistical Package for the Social Sciences 22.0 program to evaluation. To check normality, we used visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test). For categorical data we used descriptive statistics, reported counts, and proportions and we used data measures of distribution for continuous. To compare the baseline characteristics, we used an independent t test or $\chi 2$ test was performed. To assess the changes in the cross-sectional areas (CSA) of pectoralis major, pectoralis minor, and intercostal muscles and changes in the lung volumes, a 2*2 [stage (image changes in stage 1 and stage 6) * side (right or left)] repeated measures ANCOVA was performed with stage as a between-groups factor and side as a within-subjects factor, and with demographical measures set as the covariates. When the F-ratio was significant, Bonferroni's post hoc test was used to identify the mean differences. Effect sizes were determined as partial eta squared ($\eta^2 p$). The significance level was set at $p<.05$.

RESULTS

One hundred and one participants (51 female, 50 male) with the diagnosis of Covid-19 were included in our study. Clinical and demographic characteristics of the participants are presented in Table 1. The examined stages were similar with respect to most assessed basic parameters ($p>.05$). There were significant differences in body mass index scores ($p<.001$) and the obesity rate ($p<.001$), both of which were higher in stage 1.

Table 1. Demographic and clinical characteristics of participants

Variable	Stage 1	Stage 6	p
Age	51.14±14.92	-	-
Body mass index (kg/m²)	28.48±5.98	25.72±4.74	<.001
Female (n, %)	51 (50.49%)	-	-
Days from symptom onset to study protocol	-	30.12±2.41	-
Smoking rates (n, %)	17 (16.83%)	17 (16.83%)	1.00
Coexisting conditions			
Diabetes mellitus (n, %)	15 (14.85%)	15 (14.85%)	1.00
Obesity (BMI ≥ 30) (n, %)	29 (28.71%)	25 (24.75%)	<.001
Hypertension (n, %)	29 (100%)	29 (100%)	1.00
COPD (n, %)	23 (100%)	23 (100%)	1.00

Independent samples t test or χ^2 test; COPD: Chronic obstructive pulmonary disease

Table 2. Comparison of cross-sectional areas of muscles and changes in lung volume between the two stages

	Stage 1			Stage 6			2 x 2 ANCOVA	
	Right	Left	p^1	Right	Left	p^1	Side p^2 (η^2p)	Stage*Side p^2(η^2p)
PMa (cm²)	12.40±2.49	12.13±2.70	.73	11.23±2.43	11.07±2.73	.79	.677 (.002)	.314 (.010)
PMi (cm²)	4.28±0.97	4.19±1.03	.88	3.91±0.90	3.83±1.04	.85	.807 (.001)	.644 (.002)
ICM (cm²)	4.07±0.89	3.71±0.81	.12	3.84±0.86	3.50±0.81	.06	.059 (.035)	.010 (.064)*
Lung volume (cm³)	2334.30±600.16	2092.30±576.33	<.001	2238.42±632.62	2035.06±592.88	<.001	<.001 (.297)	.340 (.009)

PMa: Pectoralis major muscle; PMi: Pectoralis minor muscle; ICM: Intercostal muscle; p^1: Independent samples t test results for within-stage side comparisons; p^2: two-way repeated measures analysis of covariance with a mixed model. Figures in parentheses are effect sizes partial eta squared (η^2p).

ANCOVA revealed a significant stage*side interaction effect regarding CSA of intercostal muscle [(p=.010; η²p=.064)]. This value was smaller in stage 6 compared to stage 1 (Table 2). There was no significant difference between the two stages in terms of CSA of pectoralis major muscle [(p=.314; η²p=.010)], CSA of pectoralis minor muscle [(p=.644; η²p=.002)] and changes in the lung volume [(p=.340; η²p=.009)]. In addition, within-group analysis showed that the lung volume scores were higher for the right side both in stage 1 and 6 (p=<.001).

Figure 1. Measurement of the pectoral muscles. Cross-sectional area measurement of the pectoral muscles at the supra-aortic arteries level. PMa: Pectoralis major muscle; PMi: Pectoralis minor muscle

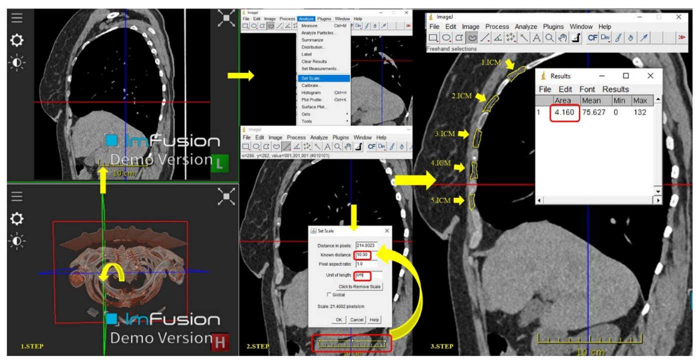

Figure 2. Measurement of the intercostal muscles. Cross-sectional area measurement of the intercostal muscles at the midclavicular line. ICM: Intercostal muscle

DISCUSSION

The primary aim of our study was to determined the potential effects of Covid-19 infection on respiratory muscles and lung volume. As a secondary objective, by scanning impaired respiratory muscle performance and lung volume we tried to provide theoretical information and propose early rehabilitation strategies to alleviate the burden on the health system during the pandemic period. Evaluating the CT images of the same patients at stage 1 and stage 6 revealed that Covid-19 pneumonia led to a decrease in the cross-sectional area of the intercostal muscles, whereas it caused no significant decrease in the cross-sectional area of the pectoral muscles nor in the lung volumes. In addition, 15% to 29% of the patients had an accompanying diagnosis of diabetes mellitus, obesity, and hypertension, indicating that people with underlying chronic diseases are more affected by Covid-19 pneumonia, as previously reported in similar studies.

Such as yawning and effective coughing behaviors are necessary to providing and maintaining pulmonary hygiene (14). This requires an optimal level of breathing together with optimal performance of the respiratory muscles. It is known that factors such as aging, smoking, obesity, chronic diseases, and physical inactivity increase respiratory workload and decrease respiratory muscle performance (15, 16). Previous studies have reported that the respiratory muscle weakness may increase the age-related decline in respiratory muscle performance in patients with multiple morbidity (16). Given the fact that the Covid-19 virus primarily affects the respiratory system and causes pneumonia, it is important to determine the impact of the infection on respiratory muscle performance. Currently, there are no studies directly investigating the effect of Covid-19 viral infection on respiratory muscles. In the present study, we obtained absolute values of the cross-sectional areas of the ICMs (as the main respiratory muscles) and the pectoral muscles (as the auxiliary respiratory muscles). The obtained data showed that Covid-19 pneumonia can cause atrophy in the respiratory muscles in a period as short as four weeks. The relationship between respiratory muscle weakness and shortness of breath is clearly demonstrated (17). Thus, we think that Covid-19-induced atrophy in the respiratory muscles may increase the risk of acute respiratory distress syndrome and respiratory failure, increasing the need for mechanical ventilation support and increasing the length of stay in the intensive care unit.

Lung volume measured on CT images, is closely related to pulmonary function test results such as forced vital and total lung capacities (18). Reduced lung volume may be an important sign of disease severity and prognosis of Covid-19 infection. Studies have reported that in severe cases of Covid-19, smaller CT lung volume is associated with alveolar collapse (6, 19). In the presented study, however, we found no significant decrease in the lung volumes between stage 1 (0-4 days) and stage 6 (>28 days). One reason could be that the lung involvement does not reach the highest level at stage 1 of the disease. Previous studies have shown that in patients with Covid-19 pneumonia, lung abnormalities on CT peak at about 10 days after the first symptoms (12). Second reason for the absence of significant lung volume difference could be the improvement of lung involvement up until the 6th stage of the disease.

The limitations of our study can be listed as following: First, lesion areas in the lungs were not evaluated. Second, prognostic data of the patients was not included due to unavailability of such data for some of the participants. Third, since physical or pulmonary performance levels of the participants were not recorded, they could not be compared with the tomographic parameters. Fourth, it was not specified from which mutations the participants were infected.

CONCLUSION

In conclusion, it can be concluded that Covid-19 pneumonia causes an atrophy in respiratory muscles. However, it seems to have a nonsignificant effect on lung volume. This indicates that despite the relation between lung volume and respiratory muscles, changes in respiratory muscle areas could occur independently of changes in lung volume. Current evidence suggests the need for further investigation of respiratory muscles and respiratory muscle training to reduce the risk of serious complications during viral infections. Moreover, the development of treatment strategies for weakened respiratory muscles may contribute to alleviating the burden on the health system during the current pandemic period.

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Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: *This study was approved by Ankara Medipol University Medical Faculty Clinical Research Ethics Committee (Registration date/no: 23.09.2021/35).*

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