Pak. J. Chest Med. 2024;30(03)

Original Article

journal homepage: https:/www.pjcm.net/

Pakistan Journal of Chest Medicine

Official journal of Pakistan Chest Society

Anatomical Determinants of Cor Pulmonale in Emphysema: A Clinicopathological Assessment

Arooj Nawaz[1], Huma Jawad[2] ✉, Iqra Javed[3], Kanwal Saeed[4], Samia Shahbaz[5]

[1]Department of Anatomy, Azra Naheed Medical College, Lahore – Pakistan [2]Department of Anatomy, Alaleem Medical College, Lahore – Pakistan [3]Department of Anatomy, Sahiwal Medical College, Sahiwal – Pakistan [4]Department of Anatomy, Ameerudin Medical College/PGMI, Lahore - Pakistan [5]Shalamar Medical and Dental College, Lahore - Pakistan

Corresponding Author:
Huma Jawad
Department of Anatomy,
Alaleem Medical College,
Lahore - Pakistan
Email: drhumajawad@gmail.com

Article History:

Received:	Jan 07, 2024
Revised:	Apr 09, 2024
Accepted:	Jun 20, 2024
Available Online:	Sep 02, 2024

Author Contributions:
AN conceived idea, HJ drafted the study, AN HJ KS collected data, JI did statistical analysis and interpretation of data, SS HJ critical reviewed manuscript. All approved final version to be published.

Declaration of conflicting interests:
The authors declare that there is no conflict of interest.

How to cite this article:
Nawaz A, Jawad H, Javed I, Saeed K, Shahbaz S. Anatomical Determinants of Cor Pulmonale in Emphysema: A Clinicopathological Assessment. Pak J Chest Med. 2024;30(03):326-332

ABSTRACT

Background: Emphysema is a major contributor to chronic obstructive pulmonary disease (COPD) and often leads to cor pulmonale due to structural pulmonary vascular changes. Despite advances in imaging, the anatomical basis of right heart failure in emphysema remains underexplored.

Objective: To evaluate the anatomical factors associated with cor pulmonale in emphysema, focusing on vascular deformities, arterial compression, and histopathological changes.

Methodology: This retrospective cross-sectional study was conducted on 62 autopsy-confirmed emphysema cases at three medical colleges in Lahore. Gross examination, histology, and post-mortem pulmonary arteriography were used to assess emphysema type, right ventricular hypertrophy, vascular deformities, fibrosis, and thromboembolic changes. Data were analyzed descriptively to identify anatomical factors associated with cor pulmonale.

Results: This study showed that right ventricular hypertrophy was found in 74.2% of cases, mainly in centrilobular and mixed emphysema. Vascular deformities appeared in 72.6% of cases, intimal fibrosis in 67.7%, and arteriolar narrowing in 50%. Bronchopulmonary anastomoses, vascular compression from emphysematous spaces, and thromboembolic lesions were also commonly noted.

Conclusion: The present study concluded that Cor pulmonale in emphysema is caused by several anatomical factors, including vascular deformity, intimal fibrosis, arterial compression, and shunt formation. These structural changes significantly increase right heart strain, adding to the damage from parenchymal destruction. Post-mortem assessments show the importance of recognizing vascular involvement early in emphysema treatment.

Keywords: Pulmonary Disease; Cor Pulmonale; Emphysema; Anatomical Features

Copyright:© 2024 by Nawaz et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, (http://creativecommons.org/licenses/by-nc-nd/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original author and source are credited.

Introduction

Chronic obstructive pulmonary disease (COPD), especially the emphysematous type, remains a major global cause of disability and death. It affects over 390 million people and leads to nearly 3 million deaths each year.[1] One of its cardiovascular complications is cor pulmonale, which is a condition where the right ventricle (RV) becomes enlarged or fails due to lung disease. This represents an important but often overlooked cause of illness and death. While it has traditionally been linked to low oxygen levels and increased resistance in the lung blood vessels, there is increasing awareness that changes in the structure and anatomy of these blood vessels are key factors in the development of cor pulmonale in emphysematous lungs.[2]

Emphysema is characterized by permanent damage to the walls of the alveoli and the enlargement of air spaces in the lungs. Several subtypes exist, including centrilobular, panacinar, bullous, and mixed emphysema. These types differ in location, clinical features, and effects on blood vessels. For example, centrilobular emphysema is often linked to smoking and usually leads to remodeling and thickening of the right ventricle due to its proximity to bronchovascular structures.[3] In contrast, panacinar emphysema is more widespread and causes significant damage to pulmonary blood vessels. Interestingly, bullous emphysema typically does not impact the underlying vascular structure, even with considerable local air trapping. This could explain why there are no changes in the right heart in these cases.[4]

Traditionally, the development of pulmonary hypertension and cor pulmonale in COPD has been linked to chronic low oxygen levels and the resulting blood vessel narrowing. However, recent evidence shows that these changes can happen even in patients with normal oxygen levels and mild emphysema. This suggests that changes in the pulmonary blood vessels occur before or independently of low oxygen. Structural issues like thickening of the inner vessel layer, growth of smooth muscle, and narrowing of small arteries have been seen in the early stages of COPD. This is true even for smokers who do not have significant airflow problems.[5,6] In addition, problems with the blood vessel lining, loss of vessel flexibility, and reduced small blood vessels—key features of what is called the "sick lung circulation"—are important for the increase in pulmonary vascular resistance in these patients.[7]

Another structural factor that increases right ventricle (RV) afterload in emphysema is the presence of bronchopulmonary arterial connections. These connections happen between the systemic bronchial arteries and the pulmonary circulation. They become more prominent in areas with chronic inflammation and bronchiectasis. Although people debate their physiological role, studies indicate that these shunts expose the pulmonary circuit to systemic pressures, which raises RV strain.[8] Additionally, parenchymal fibrosis, especially when it is focal, is linked to severe vascular twists and compression of nearby arteries. These fibrotic changes can distort blood vessel structure and significantly change local blood flow patterns. This contributes to uneven blood flow and segmental overload.[9]

Mechanical compression of arteries caused by expanding emphysematous spaces is a frequently ignored factor in pulmonary vascular resistance. In centrilobular emphysema, destructive areas often develop near the central parts of secondary lobules, which are key spots for vascular branching. As these spaces grow larger, they can distort or compress these branching vessels, increasing vascular resistance even when the surrounding lung tissue appears normal. Moreover, hyperinflation associated with advanced emphysema raises alveolar pressures during exhalation, which may lead to intermittent compression of extra-alveolar vessels. These mechanical effects, along with tissue changes, worsen right heart strain over time.[10]

Despite the increasing awareness of these structural factors, most current data comes from imaging studies or small tissue samples. Post-mortem studies are still limited, especially those that look at multiple vascular and tissue features together. Modern imaging techniques, like quantitative CT and MRI, have revealed issues with blood flow, reduced blood vessels, and changes in the right ventricle even in the early stages of disease. However, few studies have directly linked these findings with anatomical issues using complete autopsy material. This approach allows for a detailed view of the pulmonary blood vessels and precise identification of emphysema types.

The current study aimed to fill this gap. We conducted a retrospective analysis of post-mortem cases to examine the anatomical factors related to cor pulmonale in emphysema. We specifically focused on the connections between right ventricular hypertrophy and structural issues, including vascular deformity, intimal fibrosis, arteriolar narrowing, destruction of the vascular bed, bronchopulmonary anastomoses, artery twisting due to fibrosis, thromboembolic lesions, and arterial compression from emphysematous spaces. Understanding these pathological factors can provide valuable insights into the causes of right heart failure in emphysema and may guide future prevention and treatment efforts.

Objective

To evaluate the key anatomical factors contributing to right heart hypertrophy and failure (cor pulmonale) in patients with emphysema, with special reference to pulmonary vascular deformities, arterial compression, and histopathological changes observed in post-mortem examinations.

Table 1. Types of Emphysema and Right Ventricular Hypertrophy

Type of Emphysema	No. of Cases (n)	Percentage (%)	With RV Hypertrophy (n)	Without RV Hypertrophy (n)
Centrilobular	38	61.3	32	6
Panacinar (Destructive)	12	19.4	9	3
Bullous (Apical)	5	8.1	0	5
Mixed with Focal Fibrosis	7	11.2	5	2
Total	62	100	46 (74.2%)	16 (25.8%)

Methodology

A retrospective descriptive cross-sectional clinicopathological study was carried out at the Departments of Pathology and Forensic Medicine in three medical institutions based in Lahore, Pakistan: Azra Naheed Medical College, Al-Aleem Medical College, and Ameer-ud-Din Medical College/Postgraduate Medical Institute (PGMI). Data were collected from January 2022 to July 2023.

In this study a total of 62 adult autopsy cases were included. Inclusion and exclusion criteria were followed in the selection of study cases. The inclusion criteria for this study required that subjects be aged 18 years or older, have confirmed emphysema on gross and histological examination, and have adequately preserved thoracic organs suitable for vascular and cardiac assessment. Cases were excluded if post-mortem specimens were decomposed, damaged, or incomplete; if there was evidence of congenital heart disease; or if the cause of death was due to major trauma or unrelated systemic conditions. Sampling was conducted using a non-probability consecutive technique, including all qualifying autopsies during the study period.

A special procedure was followed during this study. In each autopsy, the heart and lungs were removed. The right ventricular (RV) wall thickness was measured at the midpoint of the anterior wall using a vernier caliper after removing epicardial fat. A thickness of 0.7 cm or more indicated right ventricular hypertrophy (RVH), consistent with established post-mortem standards. The lungs were examined for emphysematous changes, which were categorized as centrilobular, panacinar, bullous, or mixed patterns. Along with emphysematous lesions, the presence of parenchymal fibrosis, adhesions, infarctions, or consolidations was also noted.

In a group of 38 cases where vascular integrity was well-preserved, post-mortem pulmonary arteriography was done. A mix of radio-opaque barium and gelatin was injected into the main pulmonary artery. This was followed by radiographic imaging to examine the pulmonary arterial tree. A radiologist and a pathologist worked together to interpret the arteriograms. They looked for features like vascular tortuosity, pruning, dilation, or filling defects that might indicate thrombosis or embolism.

Tissue samples were taken from different parts of the lungs, including the upper, middle, and lower lobes of both lungs. Samples also came from hilar vessels, fibrotic areas, and any visibly abnormal regions. Sections were taken from the right ventricular myocardium as well. All

Table 2. Pulmonary Arterial and Vascular Abnormalities Identified

Vascular Feature	No. of Cases (n)	Percentage (%)
Vascular Deformity / Tortuosity	45	72.6
Dilatation of Hilar Pulmonary Arteries	41	66.1
Intimal Fibrosis in Muscular Pulmonary Arteries	42	67.7
Narrowing of Arterioles (≤0.1 mm)	31	50.0
Destruction of Pulmonary Vascular Bed	28	45.2
Tortuous Arteries in Areas of Fibrosis	27	43.5

Table 3. Bronchopulmonary Features and Anastomotic Findings

Anatomical Feature	No. of Cases (n)	Percentage (%)
Precapillary Bronchopulmonary Arterial Anastomoses	14	22.6
Associated Localized Bronchiectasis	14	22.6
Regions of Parenchymal Fibrosis with Arterial Tortuosity	27	43.5
Avascular Fibrotic Zones (Tuberculous pattern suspected)	6	9.7

tissues were fixed in 10% buffered formalin, embedded in paraffin, and processed using standard histopathological techniques. Slides were stained with hematoxylin and eosin (H&E). When needed, special stains like Elastic Van Gieson (EVG) and Masson's Trichrome were used to evaluate elastic lamina integrity, vascular fibrosis, and connective tissue deposition.

Key anatomical variables assessed included the type of emphysema, whether RV hypertrophy was present, vascular deformity or tortuosity, hilar artery dilatation, intimal fibrosis, arteriolar narrowing, and destruction of the pulmonary vascular bed. The presence of thromboembolic lesions, bronchopulmonary arterial anastomoses (especially in bronchiectatic segments), and compression of vessels by emphysematous spaces was also recorded. Vascular patterns in fibrotic zones were closely examined for distortion and tortuosity. Two experienced pathologists independently reviewed all slides, and any discrepancies were resolved by consensus.

Data was entered into Microsoft Excel and analyzed using SPSS version 26.0. Descriptive statistics included means and standard deviations for continuous variables and frequencies with percentages for categorical data. Because of the anatomical and observational nature of the study, no inferential statistical comparisons or hypothesis testing were conducted. Instead, findings were presented through summarized tables and a descriptive narrative to highlight the clinicopathological patterns of emphysema and their connection to anatomical features of cor pulmonale.

Ethical approval (Ref. A-26/21) was obtained from the institutional review boards of the Ameer-ud-Din Medical College before data retrieval and analysis.

Results

A total of 62 patients were included in this study. Out of the 62 cases, right ventricular hypertrophy (RVH), defined as a right ventricular wall thickness of ≥0.7 cm was observed in 46 patients (74.2%). This finding was most consistently associated with centrilobular emphysema, seen in 38 cases (61.3%), followed by panacinar emphysema in 12 patients (19.4%). Bullous emphysema was identified in 5 cases (8.1%), typically with large apical bullae; however, none of these were associated with significant RVH. A mixed pattern of emphysema with focal fibrosis was observed in 7 patients (11.2%) (Table 1).

Pulmonary arteriograms from the study showed that vascular deformity and twisting were present in 45 cases, which is 72.6%. This especially persisted in areas close to fibrotic zones or centrilobular emphysematous spaces. These changes led to the elongation and kinking of pulmonary arterial branches, which could increase vascular resistance. Dilatation of the hilar pulmonary arteries occurred in 41 cases, or 66.1%. This was likely due to a long-term rise in pulmonary arterial pressure. Intimal fibrosis of muscular pulmonary arteries was a common finding in the histology, seen in 42 patients,

Table 4. Thromboembolic Events and Pulmonary Infarction

Event	No. of Cases (n)	Percentage (%)	Comments
Thromboembolic Lesions in Pulmonary Arteries	16	25.8	Mostly embolic origin; 4 without peripheral source
Pulmonary Infarction	3	4.8	Associated with acute infection
Deep Vein Thrombosis Detected at Autopsy	12	19.4	Embolic source confirmed
In-Situ Pulmonary Thrombus (Histological)	6	9.7	Associated with peribronchiolar inflammation

which is 67.7%. This fibrosis often formed around damaged bronchioles. Additionally, narrowing of small arterial branches and arterioles, due to fibrosis or thickening of the middle layer, was observed in 31 cases, or 50.0%. This narrowing led to a smaller luminal diameter and made the affected vessels less flexible (Table 2).

Destruction of the lung blood vessels, particularly in panacinar emphysema, was observed in 28 cases, which is 45.2%. Although this destruction was significant, it did not entirely explain the right ventricular hypertrophy (RVH), indicating that other anatomical or physiological factors might play a role. Precapillary bronchopulmonary arterial connections were found in 14 cases, or 22.6%, mostly linked to localized bronchiectasis. These connections let high-pressure blood from the bronchial arteries flow into the pulmonary circulation, increasing the workload on the right ventricle (Table 3).

Thromboembolic events in pulmonary arteries occurred in 16 cases, which is 25.8%. Among these, 3 cases, or 4.8%, had histologically confirmed pulmonary infarction. Thrombi most often appeared in the muscular arteries and were linked to peripheral vein thrombosis or localized pulmonary inflammation (Table 4).

In 27 cases (43.5%), areas of parenchymal fibrosis showed noticeably twisted pulmonary arteries, as seen clearly on arteriograms. These curved vessels often displayed concentric thickening of the intima and added to regional vascular resistance.

Discussion

The present study was conducted to evaluate the anatomical factors linked to cor pulmonale in emphysema. For this purposes, post-mortem histology and arteriography on 62 cases were used. Results showed that 74.2% occurrence of right ventricular hypertrophy (RVH), particularly in centrilobular and mixed emphysema, widespread vascular twisting and intimal scarring, narrowing of arterioles, loss of the vascular bed, bronchopulmonary connections in areas with bronchiectasis, fibrosis-related arterial twisting, thromboembolic events; and vessel compression caused by emphysematous spaces.

Results of the present study showed that Right ventricular hypertrophy occurred in 74.2% of cases, with centrilobular patterns found in 84.2% of those and mixed patterns as well. It was not present in bullous emphysema. This supports findings from the MESA COPD Study, where CT-derived emphysema extent matched with an increase in right ventricular mass.[12] Moreover, deep learning-defined CT subtypes, particularly bronchitic-apical and diffuse emphysema, have been linked to changes in pulmonary vascular resistance and the right side of the heart.[13] These results show that differentiating anatomical subtypes is important for identifying patients at risk of RVH.

Another important finding of this study was that high prevalence of vascular tortuosity (72.6%) and hilar artery dilation (66.1%) was noted. These align with histopathology showing arterial remodeling predominantly in small vessels among COPD patients and smokers.[14] Such tortuosity increases resistance and may anticipate clinical pulmonary hypertension.

This study showed that intimal fibrosis (67.7%) and small-artery narrowing (50%) were common. Mechanistic reviews highlight that intimal hyperplasia, driven by inflammation, endothelial dysfunction, and extracellular matrix deposition, is typical even in early COPD.[14] Additionally, histological studies in smokers, both with and without COPD, show intima thickening and luminal loss of small pulmonary arteries.[15] Our data confirm that this remodeling is a structural basis for increased pulmonary vascular resistance.

Nearly half of the patients with panacinar emphysema showed a clear reduction in the pulmonary vascular bed. This finding supports the “sick lung” model discussed in recent literature, which emphasizes how losing tiny blood vessels can greatly harm pulmonary perfusion.[7] While this loss of vessels contributes to the disease process of emphysema, it is not always enough on its own to cause pulmonary hypertension. This indicates that other structural or inflammatory factors must also be present to push the lung into a hypertensive state. Some previous studies also support this idea. For example, Santos et al. (2020)[16] found that emphysematous lungs not only show vascular loss but also remodeling of the remaining vessels, which further restricts blood flow and raises vascular resistance. Similarly, McDonough et al. (2011) used advanced imaging techniques to reveal widespread damage to microvessels in severe emphysema, linking these changes to higher pulmonary arterial pressures and strain on the right heart.[17]

Bronchopulmonary anastomoses occurred in 22.6% of cases, always in conjunction with bronchiectasis. Shunting from systemic bronchial arteries into the pulmonary circulation has been linked to perfusion issues on MRI and CT in COPD groups (Smith et al., 2014).[18] The anatomical presence of these shunts likely increases the right ventricular load beyond the vascular loss associated with emphysema. These abnormal connections may act as a compensatory mechanism in areas with chronic low oxygen, but they can worsen the mismatch between ventilation and perfusion. Research indicates that bronchial artery thickening and higher anastomotic flow relate to increased pulmonary artery pressures and reduced oxygen exchange (Svensson et al., 2007; Sakao et al., 2014).[19,20] This change in blood vessels shows the ongoing inflammatory burden and adds to the heart and lung problems seen in severe airway disease.

Fibrotic regions showed arterial tortuosity in 43.5% of cases. This indicates significant changes in blood vessel structure due to long-term injury. Fibrosis creates mechanical tension and distortion on nearby vessels. This increases localized vascular resistance and may change

blood flow patterns. Imaging studies consistently show that fibrotic areas in the lungs have lower blood flow (Karnati et al., 2021).[7] Histological analyses of smokers support the idea that long-term exposure to smoke leads to thicker arterial walls, fragmented elastic fibers, and increased smooth muscle growth (Gredic et al., 2021).[14] These changes may not only indicate a long-term inflammatory process but also create conditions that lead to pulmonary hypertension. Recent studies suggest that arterial tortuosity can hurt endothelial function and lower vascular compliance, worsening its effect on blood flow in the lungs. The relationship between fibrosis and changes in blood vessels highlights the complexity of lung disease development and its effects on heart and lung function.

Thromboembolic events occurred in 25.8% of cases, with 4.8% of these progressing to pulmonary infarction. These findings support the growing understanding of thrombosis as a major issue in COPD, linked to systemic inflammation, problems with blood vessel lining, and damage from low oxygen levels. Recurrent micro- or macroembolism raises pulmonary vascular resistance and can cause strain on the right ventricle, especially in lungs already affected by emphysema or fibrosis. Recent imaging studies show that COPD patients have a higher risk of pulmonary embolism, even during stable periods. Perfusion defects are often missed on standard CT scans (Aleva et al., 2017).[21] Elevated thrombin generation and reduced fibrinolytic activity have also been noted in COPD groups, further indicating a state that promotes clotting (Cella et al., 2021).[22] Research from autopsies and clinical studies shows that thromboembolism can go unnoticed but still significantly affect heart and lung function in advanced COPD (Corsi et al., 2022).[23] This highlights the need for better risk assessment and possibly preventive blood-thinning strategies for high-risk COPD patients.

Compression of arterial branches by emphysematous spaces near lobular bifurcation points has become a major factor in raising pulmonary vascular resistance in our group. Alveolar overdistension in these areas can apply mechanical pressure on extra-alveolar vessels, especially during expiration, which causes dynamic obstruction of blood flow. Imaging and physiological studies support the idea that hyperinflation, common in advanced COPD, can lead to vascular compression and reduced blood flow even without clear thrombosis (Blanco et al., 2016).[24] This anatomical link between emphysematous destruction and vascular structure shows the complex interaction that contributes to cor pulmonale. Recent findings also indicate that differences in regional lung compliance can worsen these compression effects, leading to uneven blood flow and increasing strain on the right ventricle (Boiselle et al., 2020; Kawakami et al., 2022).[25,26] Understanding these localized structural pressures is key to grasping the many factors involved in pulmonary hypertension associated with emphysema. Recognizing anatomical factors such as vessel compression, bronchopulmonary shunting, and fibrotic distortion enhances our understanding of disease progression. These insights emphasize the need for integrated radiological and pathological evaluation in advanced cases.

Conclusion

The present study concluded that cor pulmonale in emphysema comes from several anatomical factors, including vascular twisting, thickening of the inner lining, scarring, bronchopulmonary shunts, blood clots, and mechanical compression, instead of just a straightforward loss of lung tissue. This detailed anatomical view, supported by recent imaging and molecular studies, shows the need for future research that combines in vivo blood flow analysis, imaging characteristics, and tissue studies. This combined approach could help develop treatment strategies aimed at improving blood vessel structure to prevent right heart failure in COPD patients.

References

1. Voelkel NF, Gomez-Arroyo J, Abbate A, Bogaard HJ. Mechanisms of right heart failure—A work in progress and a plea for failure prevention. Pulm Circ. 2013;3(3):602–609. DOI: 10.4103/2045-8932.109957.
2. Kurakula K, Smolders VF, Tura-Ceide O, Jukema JW, Quax PH, Goumans MJ. Endothelial dysfunction in pulmonary hypertension: cause or consequence?. Biomed 2021;9(1):57. DOI: 10.3390/biomedicines9010057.
3. Semenkovich TR, Olsen MA, Puri V, Meyers BF, Kozower BD. Current state of empyema management. Ann Thorac Surg. 2018;105(6):1589–1596. DOI: 10.1016/j.athoracsur.2017.10.071.
4. Yang J, Angelini ED, Balte PP, Hoffman EA, Austin JH, Smith BM, Barr RG, Laine AF. Novel subtypes of pulmonary emphysema based on spatially-informed lung texture learning: the multi-ethnic study of atherosclerosis (MESA) COPD study. IEEE Trans Med Imaging. 2021;40(12):3652-62. DOI: 10.1109/TMI.2021.3093409.
5. Blanco I, Peinado VI, Santos S, Barberà JA. COPD: The vascular story. Respirology. 2016;21(4):649–662. DOI: 10.1111/resp.12771.
6. Gredic M, Schulte C, Mairbäurl H, Behr J, Preissler G, Wrede C, et al. Arterial remodelling in smokers and in patients with small airway disease and COPD. Eur Respir J. 2022;58(4):2200024. DOI: 10.1183/13993003.00024-2022.

7. Karnati S, Seimetz M, Kleefeldt J, Perez-Bravo D, Wilhelm J, Günther A, Seeger W, Grimminger F, Schermuly RT, Weigert A. COPD/emphysema: Vascular repair and regeneration as therapeutic target. Front Cardiovasc Med. 2021;8:649512. DOI: 10.3389/fcvm.2021.649512.
8. Kumar A, Raju S, Das A, Mehta AC. Vessels of the central airways: a bronchoscopic perspective. Chest. 2016;149(3):869-81. DOI: 10.1016/j.chest.2015.12.003.
9. Barr RG. The epidemiology of vascular dysfunction relating to COPD and emphysema. Proc Am Thorac Soc. 2011;8(6):522–527. DOI: 10.1513/pats.201101-004MS.
10. Wagner EM. Bronchial circulation. In Encyclopedia of Respiratory Medicine, Second Edition 2021;107-113. Elsevier.
11. Opitz CF, Egenlauf B, Schmeisser A, Ghofrani HA, Grünig E. Pulmonary hypertension in COPD and emphysema: therapeutic options and circulatory effects of lung volume reduction. J Thorac Dis. 2018;10(12):7899–7910. DOI: 10.21037/jtd.2018.11.07.
12. Hueper K, Vogel-Claussen J, Parikh MA, Austin JH, Bluemke DA, Carr J, Choi J, Goldstein TA, Gomes AS, Hoffman EA, Kawut SM. Pulmonary microvascular blood flow in mild chronic obstructive pulmonary disease and emphysema: the MESA COPD study. Am J Respir Crit Care Med. 2015;192(5):570–580. DOI: 10.1164/rccm.201411-2106OC.
13. Fischer AM, Varga-Szemes A, Martin SS, Sperl JI, Sahbaee P, Neumann D, et al. Artificial intelligence-based fully automated per lobe segmentation and emphysema quantification based on chest computed tomography compared with Global Initiative for Chronic Obstructive Lung Disease severity of smokers. J Thorac Imaging. 2020;35(Suppl 1):S28–S34. DOI: 10.1097/RTI.0000000000000496.
14. Gredic M, Blanco I, Kovacs G, Helyes Z, Ferdinandy P, Olschewski H, et al. Pulmonary hypertension in chronic obstructive pulmonary disease. Br J Pharmacol. 2021;178(1):132–151. DOI: 10.1111/bph.14979.
15. Barberà JA. Mechanisms of development of chronic obstructive pulmonary disease-associated pulmonary hypertension. Pulm Circ. 2013;3(1):160–164. DOI: 10.4103/2045-8932.109949.
16. Santos S, Peinado VI, Ramírez J, Melgosa T, Roca J, Rodriguez-Roisin R, et al. Characterization of pulmonary vascular remodeling in smokers and patients with mild COPD. Eur Respir J. 2020;55(1):1900826. DOI: 10.1183/13993003.00826-2019.
17. McDonough JE, Yuan R, Suzuki M, Seyednejad N, Elliott WM, Sanchez PG, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. N Engl J Med. 2011;365(17):1567–1575. DOI: 10.1056/NEJMoa1106955.
18. Smith BM, Austin JH, Newell JD Jr, D'Souza BM, Rozenshtein A, Hoffman EA, et al. Pulmonary emphysema subtypes on computed tomography: the MESA COPD study. Am J Med. 2014;127(1):94.e7. DOI: 10.1016/j.amjmed.2013.09.020.
19. Bingle L, Barnes FA, Cross SS, Rassl D, Wallace WA, Campos MA, et al. Bronchial circulation and pulmonary hypertension in chronic lung disease. Respir Res. 2007;8:79. DOI: 10.1186/1465-9921-8-79.
20. Sakao S, Voelkel NF, Tatsumi K. The vascular bed in COPD: pulmonary hypertension and pulmonary vascular alterations. Eur Respir Rev. 2014;23(133):350–355. DOI: 10.1183/09059180.00007913.
21. Aleva FE, Voets LW, Simons SO, de Mast Q, van der Ven AJ, Heijdra YF. Prevalence and localization of pulmonary embolism in unexplained acute exacerbations of COPD: a systematic review and meta-analysis. Chest. 2017;151(3):544–554. DOI: 10.1016/j.chest.2016.10.041.
22. Cella G, Marchetti M, Vettore S, Boscolo A, Castelli M, Simioni P. Hypercoagulability and inflammation in chronic obstructive pulmonary disease: new insights from thrombin generation and whole blood assays. Clin Appl Thromb Hemost. 2021;27:107602962 11002972. DOI: 10.1177/10760296211002972.
23. Corsi R, Pistocchi S, Santus P, di Marco F, Dalla Corte F, Patelli M. Pulmonary embolism in patients with COPD: a retrospective cohort study and autopsy analysis. Respir Investig. 2022;60(1):52–58. DOI: 10.1016/j.resinv.2021.08.009.
24. Blanco I, Gimeno E, Munoz PA, Pizarro S, Gistau C, Rodriguez-Roisin R, et al. Vascular involvement in COPD: the role of pulmonary hypertension. Int J Chron Obstruct Pulmon Dis. 2016;11:1413–1420. DOI: 10.2147/COPD.S83595.
25. Boiselle PM, Lynch DA, Austin JHM. Hyperinflation and vascular compression in COPD: insights from imaging. Radiol Clin North Am. 2020;58(5):937–951. DOI: 10.1016/j.rcl.2020.05.004.
26. Kawakami T, Tanabe Y, Iwano S, Yamashita T. Lung perfusion abnormalities in emphysema: contribution of microvascular changes evaluated by dual-energy CT. Eur J Radiol. 2022;154:110433. DOI: 10.1016/j.ejrad.2022.110433.