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RESEARCH ARTICLE

The Role of Small Airways in Respiratory Failure Caused by Covid-19 Infection

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ABSTRACT

Small airways are the “silent zone” of lungs because there is a limited range of methods to assess their function. At the same time this lung zone plays an important role in local distribution between ventilation and perfusion, that in turn influences the effectiveness of gas exchange. Small airways are incorporated into the lung elastic network and their patency is strongly influenced by the pathological processes that occur in lung parenchyma.

ACE2 receptors which are the bindng sites for SARS-Cov-2 virus most densly are located on the epihelium of upper airways, second type alveolocytes and club cells. Damage to mucosa of pharynx and proximal bronchi explains the symptoms of mild covid-19 disease, but affections to alveolar epthelium opens the access to pulmonary vessels which increase permeability inducing interstitial oedema, initiate infiltration of lung interstitium with inflammatory cells and release from endothelial cells vasodilatory mediators which in turn inactivate the mechanism of hypoxic pu;monary vasoconstriction.

Ventilation/perfusion mismatch in favour of perfusion that develpops as the consequence of described events leads to intrapulmonary blood shunting, arterial hypoxaemia and severe dispnoea that poorely associates with mild changes in X-ray examination findngs.

Progressing of parenchimal inflammation further increases the pulmonary vascular permeabiluty that recruits more alveoli, increases the lung weight and affects gas diffusion through alveolo-capillary membrane making hypoxemia more severe.

During the acute period of covid-19 pneumonia small airways demonstrate more functional rather than organic obstruction. However, during the post-acute period proliferation of bronchiolar epitelial cells occurs, they transdifferentiate and ingrow into alveolar space and initiate lung and airways fibrosis.

This review has summarized recent research findings that uncover the small airways role in different pathogenetic mechanisms involved in the course of covid-19 infection both in acute and recovery period.

Introduction

Small airways are called "the silent zone of lungs" because conventional diagnostic methods do not reflect pathologic changes occurring in this region [1]. Covid-19 infection has renewed interest on this silent lung zone because of unexplained severe hypoxemia that does not associate with the severity of alveolar damage observed in acute phase of disease [2], [3], and recent observations that post-Covid-19 lung fibrosis starts from trans differentiation and proliferation of bronchiolar epithelial cells [4].

Small airways are membranous bronchi with a diameter less than 2 mm that lack cartilagineos elements in their walls They are incorporated into the elastic network of lungs that supports their lumen open. When lungs expand during the inspiration the lumen of small bronchi enlarges, but during the expiration – narrows. In dependent lung areas by the end of expiration small airways even closes totally entraping the gas in alveoli. This entrapped volume of gas is named closing capacity (CC). Gas entrapment occurs under normal conditions in elderly healthy persons, but in pathologic processes that occur in lung parenchyma, like vascular congestion and parencymal oedema, compression of small airways becomes significant and it increases the CC. As well, CC changes occur in response to changes in small airways themselves, such as increase of smooth muscle tone and occlusion of the lumen by exudate, mucus, or proliferating cells [5]

Measurement of CC allows to evaluate indirectly the function of small airways by both radiologic and physiologic methods. Radiologicaly the entrapped gas volume may be detected using the quantitative inspiratory-expiratory distraction method [6]. This method has given a significant impact in understanding what happens with small airways during the acute period of SARS-CoV-2 induced pneumonia.

Application of physiological methods during the acute period of covid-19 pneumonia is restricted due to epidemiological factors and risk for self-inflicted lung injury (pSILI) [7]. Therefore, these methods have been applied mainly in studies of post-covid sequalae.

Important impact in understanding the pathogenesis of SARS-CoV-2-induced dyspnoea have given post-mortem lung studies and *in vivo* biopsy specimen examinations. In vitro studies of airways epithelial cells have given more information about SARS-CoV-2 virus binding sites [8], [9].

The present review will try to collect all the data obtained in different fields of medical science to uncover the mechanisms of dyspnoea induced by SARS-CoV-2 virus with special focus on small airways.

Search for SARS-CoV-2 binding sites

Important point to evaluate certain cells role in the pathogenesis of covid-19 pneumonia is to uncover specific virus binding sites on possible target cells. Crutial for the endocitosis of SARS-CoV-2 virus are two proteins: ACE2 and transmembrane serine proteinase 2 (TMPRSS2), a cofactor for SARS-CoV2 entry. Presence of these proteins were searched both on biopsy specimens and on cultured airways epithelial cells. In airways biopsy specimens ACE2 protein was highest within regions of the sinonasal cavity and bronchioles. In the lung parenchyma ACE2 protein was found on the apical surfaces of a small subset of alveolar type II cells and was colocalized with TMPRSS2 [10].

Additionally other studies reported that ACE2 protein was more abundantly expressed on the apical than the basolateral surface of polarized airway epithelia. Interestingly, ACE2 expression positively correlated with the differentiation state of epithelia. Undifferentiated cells expressing little ACE2 were poorly infected with SARS-CoV-2, while well-differentiated cells expressing more ACE2 were readily infected.[11].

In airways epithelium ACE2-protein expression was significantly higher in club cells compared to other epithelial cells (including ciliated cells, basal cells, goblet cells, neuroendocrine cells, and alveolar type 2 cells). Besides it, numbers of club cells in bronchiolar epithelium and ACE2-positive club cells were significantly more in COPD patients compared to controls that explains increased susceptibility of these patients to covid-19 infection [12].

In studies using RNA sequencing transcriptome profiling of samples of airway and oral mucosa led to similar findings. Medium levels of ACE2 expression was found both in small airways epithelium and masticatory mucosa, and high levels of expression in nasal epithelium. TMPRSS2 was highly expressed in small airways epithelium and nasal epithelium and has lower expression in masticatory mucosa. Authors concluded that the nasal mucosa is the most susceptible locus in the respiratory tract for SARS-CoV-2 infection [13].

Furthermore, Chen at al studied the expression of ACE2 protein both on natural bronchial epithelial cells obtained during airways biopsies and human airway basal epithelial cells cultured at air-liquid interface (ALI). Both cultured basal cells at ALI and airways cells obtained from biopsies retained the capacity to differentiate into ciliated, club and goblet cells. ACE2 and TMPRSS2 were mainly localized to ciliated and basal epithelial cells in human airway biopsies, ALI, and airways organoids [14].

The expression of ACE2 receptors was studied also on isolated human airway smooth muscle (ASM) cells from normal males versus females to explain, why covid infection predominate in males. Using confocal imaging, researchers found that ACE2 is expressed in human ASM. Furthermore, Western analysis of ASM cell lysates showed significantly lower ACE2 expression in females compared with males at baseline [15].

The presence of specific binding sites for SARS-Cov-2 spike proteins on upper airways epithelium explains typical early symptoms of Covid-19 infection – dry cough and sore throat. In mild cases, the infection may not affect the alveolar area [16].

ACE2 receptor has enzymatic activity and detach one amino acid from both ATI and ATII molecules producing AT 1-9 and AT1-7 molecules respectively. These short angiotensin molecules exert their actions via activation of Mas receptor inducing distinct from ATII effects, such as vasodilation, anti-inflammatory and antithrombotic activities [17].

So, ACE2 damage induced by SARS-CoV-2 virus increases the action of ATII. As the result triple of change occur: surfactant loss, edema and excess of ATII that tends small airways to collapse. It manifests as more early airways closure during the course of expiration with air trapping, or by development of atelectasis in some lung areas [18].

Whether atelectasis will induce the blood shunting depends on the balance of locally released and circulating vasodilating and vasoconstricting mediators that regulate the HPV [19, 20].

Pathohistological data

Majority of Covid-19 pathomorphologic studies were performed on post-mortem specimens and therefore reflected the affections that are characteristic for most severe course of disease. One of the first comprehensive reports on autopsy results of covid-19 victims was a joint US-Italian study of 68 autopsies from 3 institutions in heavily hit areas (2 USA, 1 Italy). Authors found that tracheobronchitis was frequently present, diffuse alveolar damage (DAD) was seen in 87% of cases. Large vessel thrombi were seen in 42% of cases but platelet (CD61 positive) and/or fibrin microthrombi were present at least focally in 84%. Ultrastructurally, small vessels showed basal membrane reduplication and significant endothelial swelling with cytoplasmic vacuolization. In a subset of cases, virus was detected using different tools [21].

Other studies confirmed major involvement of pulmonary vasculature. These included severe endothelial injury, alveolar-capillary microthrombi [22], venous thromboembolism [23].

In order to get an insight in the sequence of changes that develop during the course of disease Mauad and colleagues evaluated the morphological changes in autopsy specimens relative to the period between admittance to hospital and the moment of death. They reported that vascular affections developed early in the disease and manifested with endothelial damage and microvascular thrombosis which was present in 90% of all patients. Diffuse alveolar damage (DAD) progressed more slowly and developed its maximum in the late period, longer than 17 days [24].

Stoyanov et al as well reported that exudative process in parenchyma, induced by increased vascular permeability, dominated in early period of the disease and it associated with two-fold increase of lung mass reaching in average 1040 g. During the proliferative period lung mass tended to decrease but instead hyaline membranes appeared in alveoli and massive hyperplasia of alveolar type II cells took place. Additionally in respiratory bronchioles club cell proliferation was observed [25].

Club cells are secretory cells that are highly prevalent in bronchioles. They are cubical in shape, they lack cilia and constitute in human lungs approximately 9% of the total population of airway epithelial cells; Approximately 11-22% of CCs are located in the terminal bronchioles. [26] Club cells participate in the biotransformation of many harmful and toxic compounds introduced to the lungs with inhaled air, they secrete proteins which bind the surfactant, stabilizing its structure and they serve as progenitor cells for both themselves and ciliated cells [27].

Appproaches for *in vivo* diagnostics of SARS-CoV-2-induced morphologic changes

Reports on morphologic changes in mild and moderate course of disease are scant. Doglioni and associates examined 12 Covid-19 patients by transbronchial lung criobiopsy within 20 days of symptom onset. They reported on spots of patchy acute lung injury with alveolar type II cell hyperplasia, with no evidence of hyaline membranes. Interalveolar capillaries showed enlarged lumen and were in part arranged in superposed rows. Pulmonary venules were characterized by luminal enlargement, thickened walls, and perivascular CD4+ T-cell infiltration These changes were different from those found in classical interstitial lung disease (ILD) and diffuse alveolar damage and demonstrated the severe derangement of immune mechanisms triggered even early on in the viral infection. The condition of airways in this report was not described [28]

Radiological examinations of lungs performed during acute period of the coronavirus disease

typically are characterized by ground glass attenuations (GGA) suggesting vascular and parenchymal involvement. Vessel enlargement has been described in the vicinity of areas with ground-glass opacities, which suggests thrombo-inflammatory processes. Subsegmental vascular enlargement (more than 3 mm diameter) in areas of parenchymal lung opacities has been observed in 89% of patients with confirmed COVID-19 pneumonia. Although *in situ* thrombosis is certainly a possibility, these findings could reflect hyperaemia and increased blood flow due to pro-inflammatory factors and vasoplegia induced by SARS-CoV-2 [29].

Special radiological approaches, like Inspiratory to expiratory CT distraction method allows to get additional data about small airways behavior during the acute covid-19 pneumonia period. This method is aimed to measure the volume of entrapped air at the end of expiration, when part of small airways becomes closed by forces that tend airways to collapse. Standardized non-contrast chest CT imaging is performed by obtaining an inspiratory scan at total lung capacity (TLC) and an expiratory scan at residual volume (RV), Method quantifies the voxel-to-voxel difference in Hounsfield units between matched inspiratory and expiratory images to estimate the probability of air trapping. Probability is inversely proportional to the relative differences in Hounsfield units [6].

Dual energy CT method allows to obtain lung images which distinguish three compartments: shunt (non-aerated but perfused lung regions), dead space (aerated, non-perfused regions), and non-aerated/non-perfused areas. Gas to blood volume can be computed that reflects the proportion of matched gas and blood distribution expressed as percent of the total lung mass.[30].

Lung function examination during the acute stage of the disease

Options for assessing lung function during the acute period of the disease are limited due to epidemiologic restrictions and due to patients condition. Deep inspirations and forced expirations necessary for standard spirographic examination are dangerous for patient, because of possible lung damage by self-inflicted lung injury (SILI) [7].

However, thanks to the possibilities provided by the recently developed portable FOT equipment it became possible to study small airways during the acute period of covid-19 pneumonia. Method allows to measure airways resistance and reactance without patient's active participation and get information about small airways.

During the hospital stay we monitored the changes in small airways on 30 oxygen dependent patients and found indices of significantly elevated resistance of small airways in 65% of patients. Increased resistance data correlated significantly with patient's oxygen demand and with the duration of hospital stay. 3 months after the discharge from the hospital for repeated control arrived 18 patients. During the hospital stay 11 of them had obstruction of small airways. After 3 months obstruction was still present in 5 persons. [Taivans et al, in press].

Presence of air trapping during acute period of the SARS-CoV-2 infection reported also Huang and associates as the part of their retrospective study of CT images performed during the course of Covid-19 patients intrahospital treatment and consequent 2-month folow-up. They analysed inspiratory and expiratory chest high-resolution CT images. Study included 108 patients who were divided into three groups according to the time interval between the onset of symptoms and initial CT. Researchers concluded that air trapping was more distinguished in the early stage of the disease and persisted during the 2-month follow-up.[31].

Taken all available data together can be concluded that during the acute period of covid -19 pneumonia dominate the signs of vasoplegia, increased vascular permrability with consequent parenchimal edema and thrombosis. Observed obstruction of small airways occurs due to their compression from congested parenchima and partially by increased bronchial smooth muscle tone induced by inflammatory cytokines.

Post covid sequelae

According to WHO statement from 2021 10-20% of covid-19 survivors develop long covid which manifests with wide range of symptoms reflecting the involvement of multiple body systems including lungs.

In a prospective, multicentre, observational follow-up study of patients admitted for bilateral COVID-19 pneumonia in 12 hospitals in Spain were included 488 persons. Pulmonary functional outcomes and chest computed tomography sequelae were analyzed 12 months after hospital discharge. Patients were classified into three groups according to severity. The evaluation revealed that severe patients had statistically worse levels of lung diffusion at 2 months, but no between group differences were found in subsequent controls. Impaired lung diffusion was found in 40% unrelated to severity, but radiological fibrotic-like changes were reported in 23% of patients. Authors concluded that significant percentage of individuals would develop pulmonary sequelae after COVID 19 pneumonia, regardless of severity of the acute process [32].

Franquet et al. studied 48 long covid-19 patients on a median of 72.5 days after the onset of symptoms by thin-section CT and found that air trapping was present in 77%, bronchial wall thickening in13% and traction bronchiectasis - in 19% of cases, whereas parenchimal abnormality was found in 50% of patients. Authors concluded that in long-COVID patients with persistent respiratory symptoms the most common finding is air trapping [33].

Also, Jia et al. evaluating 205 COVID-19 survivors by quantitative inspiratory-expiratory chest CT (QCT) during 6-month follow-up found the air trapping in 29% of survivors. Air trapping was more frequently observed in the patients with lung diffusion capacity (DLco) below normal limits [34].

Using the same approach Cho et al also found air trapping in 34% of hospital treated patients 30 days following diagnosis [35].

Important points in mentioned observations are independence of pulmonary sequalae from the severity of the acute process and signs of air trapping that are still present even a year after the onset of the disease.

Air trapping in lungs as described previously is a physiological event that occurs due to changes of transbronchial pressure under the influence of different forces and it may not be connected with patholologic changes in bronchi. Radiologists refer to it as functional small airways disease (fSAD) [35].

One of forces tending to close bronchial lumen is bronchial smooth muscle tone. Maniscalco et al. checked bronchial reversibility in covid-19 survivors two months after the onset of the disease and found that the response to salbutamol manifested not only by FEV-1, but as well, by significant FVC improvement that allowed authors to state that 56% of examined persons had mixed obstructive-restrictive lung syndrome. Besides it, authors suggested that low lung diffusion capacity (D_{LCO}) characterizing the restrictive pattern is mainly determined by a reduced alveolar volume and not by the residual interstitial lung abnormalities or pulmonary vascular abnormalities [36].

Sequalae connected with lung remodelling

There are radiologic signs indicating on typical morphological changes that use to develop in small airways. Such are bronchiolar wall thickening, traction bronchiectasis and honeycombing. On their basis lies proliferation and transformation of both epithelial cells of airways and changes in lung parenchyma leading to fibrotic transformations.

Intraluminal changes in small airways

Intraluminal changes in small airways start gradually after two weeks with hyperplasia of club cells followed by their transformation to squamous cells, invading into alveoli and formation of intraalveolar squamous cell bulbs [25]. Also, other airways epithelial cells undergo molecular alterations typical of epithelial-to mesenchymal transitions (EMT) which results in the down-regulation of genes associated with tight junctions and so eradicate the proposed ARDS-protective effect of these epithelial, ACE2-positive cells [4].

Data obtained in studies of pathogenesis of interstitial pulmonary fibrosis (IPF) indicate on trans-differentiation of airways basal cells so that cells belonging to airways conductive zone replace alveolar epithelial cells. This process termed bronchiolization is characterized by $p63^+$ $KRT5^+$ airway epithelial-like cell types replacing the normal alveolar epithelium [37].

The multidetector CT (MDCT) specimen scans show that airways located between the 9th and 14th generations of airway branching increase their visibility in IPF due to thickening of their walls and distortion of their lumens. Small airways disease is a feature of IPF, with significant loss of terminal bronchioles occurring within regions of minimal fibrosis [38].

Certain role in fibrotic processes that develop in airways epithelium play epithelial to mesenchymal transition (EMT). During this process under the influence of pathological stimuli and cytokines such as TGF-β, ET-1,IL-1, IL-4, epithelial cells undergo trans-differentiation towards myofibroblasts which are cells secreting constituents of connective tissue such as collagens, elastin, glycoproteins and proteoglycans [39,40].

Studies on bronchial and alveolar epithelial cell cultures have shown that these cells may undergo EMT [41]. As the result of this process epithelial cells lose their typical surface recognition molecules E-cadherin, cytokeratin and obtain mesenchymal marker proteins such as collagen I, tenascin C, fibronectin and α-smooth muscle actin [39,42].

The loss of terminal bronchioles correlates with honeycomb formation and as the result conducting airways directly lead into honeycomb cysts. Early studies have demonstrated that peripheral cystic air spaces are ventilated but represent physiological dead-space because they are not perfused [43]. This supports the concept that small airways are the origin of honeycomb cysts [44].

In thoracic radiology, the term “honeycombing” refers to clustered cystic airspaces which typically are located in the subpleural region of the lung. [45] While clinical HRCT only detects honeycomb cysts with a diameter of about 1 mm and bigger, smaller honeycomb cysts are usually observed in histological examinations. Typical microscopic

honeycomb cysts are small, subpleural, and localized in vicinity to fibrotic areas[46].

Small airways remodelling induced by parenchymal changes

Another cause of small airways remodelling are the changes that occur in lung parenchyma. Transbronchial biopsies performed 4 to 15 months after the acute period of covid-19 pneumonia on patients with persistent dyspnoea revealed peribronchial remodelling with interstitial pulmonary fibrosis [47].

As can be judged from human IPF sample studies and murine models of pulmonary fibrosis, at the sites of parenchymal injury expansion of myofibroblast population occur, Single cell sequencing method allowed to distinguish four functional populations of lung fibroblasts: myofibroblasts, lipofibroblasts, matrixfibroblasts, and alveolar niche cells. In lung injury lipofibroblasts, which under normal conditions support 2nd type alveolocytes, transdifferentiate into myofibroblasts and together with residing myofibroblasts proliferate and start to produce extracellular matrix components. In both human IPF samples and murine models of pulmonary fibrosis, the myofibroblast population expands considerably [48], [49], suggesting aberrant fibrotic activation in a variety of fibroblast populations. In the bleomycin injury model, interstitial lung fibroblasts, pericytes, and mesothelial cells are known to differentiate into myofibroblasts. Partial epithelial-mesenchymal transition (EMT) has also been reported [50].

At the tissue level, IPF is defined by a fibroblastic focus with an immature hyaluronic acid-rich matrix underneath the epithelial layer, loss of alveolar type 1 cell differentiation, and increased αSMA+ myofibroblasts. The presence of epithelial basal-like cells that co-express epithelial and mesenchymal markers has been reported in IPF lungs by ssRNA-seq. These indeterminate alveolar type 2 cells were found to be located at the edge of myofibroblast foci in the IPF lung [51],[52].

In IPF concentric fibrosis encircles the bronchioles, resulting in airway narrowing or obliteration. This is termed constrictive (or obliterative) bronchiolitis. From another side, accumulation of connective tissue matrix in lung parenchyma leads to deformation of small airways and development of traction bronchiectasis.[53].

Functional manifestations of small airways remodelling

Described intraluminal and extraluminal changes in small airways affect the function of small airways in opposite ways. Intraluminal epithelial cell proliferation leads to obstructive type of ventilatory failure and enhances the air trapping. From another side. traction bronchiectasis induced by parenchymal fibrosis increases the conductance of small bronchi and manifests functionally as restrictive ventilatory failure. Both conditions may coexist in different regions of the same lung in balanced way, but as well, one pattern may dominate in a particular patient and manifest as obstructive or restrictive disorder.

As an example, Bonato and associates in 62 post-covid-19 pneumonia patients found that three months after the hospital discharge 27% of persons had exertional dyspnoea and 12% - cough. Dyspnoeic patients had a lower forced expiratory flow (FEF_{25-75}) indicative to small airways disease, while a CT scan showed that patients with cough had a higher extent of bronchiectasis [54].

Lopes et al observed 59 post-covid-19 patients for 5 months and, using classical lung function testing with spirometry, found restrictive pattern of ventilatory failure in 30% and obstructive pattern in 14% of patients one month after the discharge from the hospital. After 5 months patients status improved, and restrictive failure cases dropped to 22% and obstructive cases – to 12%. Impulse oscillometry revealed small airways obstruction in 64% of cases after one month and 55% - after 5 months. High selectivity for small airways obstruction diagnostics showed lung ultrasound examination that revealed 78% and 61% positive individuals at one- and 5-months measurements [55].

However, should be mentioned that diagnosis of restrictive pattern of ventilatory failure based on spirometry may be misleading, because of early airways closure that results in air trapping and hence, low FVC [56].

Half of the COVID-19 patients with pulmonary fibrosis (50%) who survived required oxygen therapy, and those with "honeycomb" lung required long-term oxygen therapy to a far greater extent than others [57].

The role of small airways in the pathogenesis of covid-19 pneumonia

ACE2 receptors on airways mucosa are distributed unevenly. They are most densely placed on the surface of upper airways and moderately distributed on lower airways [6],[10]. When infection occurs, the first manifestations reflect the inflammation of upper airways. By destroying airways epithelial cells infection spreads towards the periphery of lungs and infects epithelium of alveolar ducts and alveoli. ACE2 receptors have dense distribution on alveolar type II cells and club cells that line the bronchioles [10] Alveolar type II cells secrete surfactant that decreases surface tension of alveoli and bronchioles. Surfactant loss makes these structures prone to collapse. Epithelial damage from

another side opens for SARS-Cov-2 virus access to vascular endothelium inducing its damage and vasculitis [23]. Increased permeability of lung capillaries induces lung parenchymal edema that can be recognized on CT images as GGO with peripheral localization [58].

During the first stage of the disease, referred to as L type by Gattinoni et al., the lungs are characterized by low elastance, low recruitability and low ventilation to perfusion (V/Q) ratio [59].

Crutial role in ventilation and perfusion matching plays hypoxic pulmonary vasoconstriction (HPV) discovrered in 1946 by von Euler and Liljestrand [60]. In experiments on cats authors found that lung ventilation with 10% of oxygen significantly elevated pulmonary artery pressure. Following studies by Bergofsky and Holtzman in 1967 [61] performed on isolated pulmonary artery strips not only confirmed Euler's et al. data but demonstrated that this mechanism is local and distributs the blood flow from non-ventilated alveoli towards ventilated ones.

However, this mechanism may be inhibited by vasodilating inflammatory mediators, like nitric oxide (NO) and prostacyclin PgI2 [62]. Patients with ARDS exhale higher concentrations of NO than healthy controls, suggesting its pulmonary origin [63]. PGI_2 is produced in endothelial cells *via* the prostacyclin synthase and acts *via* prostaglandin I_2 receptors inducing vasodilation, anti-inflammatory effects, and decreasing platelet aggregation [64]. Besides it, HPV is inhibited by one of the most relevant cytokines, interleukin-6 (IL-6) [65].

As the result of vasoplegia, blood under the gravitational forces flow through the dependent parts of lungs which are poorely ventilated. At the same time blood vessels in upper parts of lungs, which are well ventilated, are narrowed under the influence of elevated levels of angiotensin II. It steals the vascular flow towards areas of non-aerated hyperperfused lungs [19].

As long as the course of disease is not severe, ventilation and perfusion balance is dynamic and is influenced by gravitational forces. Typical example is the effect of proning that is widely used to improve the patients oxygenation. When the body position is changed from supine to prone, blood is overdistributed from dorsal lung regions to the ventral ones. Airways and alveoli in dorsal areas reopen as they are released from compression exerted by vascular walls. It results in matching of ventilation to perfusion and prevents blood shunting through this region. This works not regarding to worsening the situation in ventral regions, because the dorsal lung area has larger volume than the ventral one [66].

Besides it, additional impact gives physiologic blood shunting through arteriovenous anastomoses which are more developed in dorsal lung areas. Masi and coleagues using the technique of transpulmonary bubble transit (TPBT). have detected the intrapulmonary arteriovenous anastomoses in 20% of patients with COVID-19 [67]. Under certain pathological conditions shunt blood flow may reach high levels. Dakin and associates found that in severe ARDS patients the shunt flow may reach up to 50% of the cardiac output [68]. Hypoxia induced by intrapulmonary blood shunting is resistent to inhalational oxygen therapy and require veno–venous extracorporeal membrane oxygenation (ECMO), that is only effective therapy in cases of intrapulmonary shnting [69].

During the course of the disease the exudative phase transorms into proliferatve one and arterial hypoxemia gets additional pathogenetic cause - affected gas diffusion due to thickening of alveolo-capillary membrane. Characteristic pathologic changes in proiferative stage of disease are hyperplasia of II-type alveolocytes and fibrin deposition. Diffuse alveolar damage (DAD) and hyaline membrane deposition are characteristic for severe course of disease [70]. In contrast to blood shunting, affected diffusion is succesfully treated with increasing the FiO2 [71].

Worsening of the disease manifests with increase of lung elastance, lung weight and lung recruitabilty which Gattinoni termed phenotype H in contrast to phenotype L manifesting with with low elastance, low lung weight, and low lung recruitability [59]. Although patients with low or high respiratory elastance may both experience severe hypoxemia, the underlying mechanisms may differ between groups. Whereas in patents with L phenotype the major pathogenetic factor is loss of HPV with consequent vasoplegia and blood shunting, In H phenotype the mean factor is increased pulmonary capillary permeability with perivascular infiltration with mononuclear cells, endotheliolitis, microvascular thrombosis. alveolar recruitment and development of DAD [23].

Intravascular occlusion by microthrombi increases the dead space and changes the ventilation/ perfusion proportion in favour of ventilation. Harbut et al. calculated shunt and alveolar dead space in covid-19 pneumonia during the acute phase and two months after the recovery. They found that during the acute period shunt volume was elevated to 10,4% of cardiac output and alveolar dead space to 14,9% of tidal volume. No correlation between two parameters was found indicating of different pathogenetic background. After two months pulmonary shunt was marginally detectable in two, but alveolar dead space was still preserved

in 30% of patients suggesting on persisting pulmonary vascular pathology [72].

Pathogenesis of dyspnoea

Breathlessness is very characteristic sign of covid-19 pneumonia, and it is caused by hypoxemia. However, patients experience of breathlessness do not correlate directly with the level of hypoxemia, even more – some patients do not complain on shortness of breath despite low arterial oxygen level. Huang et al reported that the prevalence of breathlessness was as high as 92% amongst patients hospitalized in intensive care units versus only 37% in patients in non-intensive care units [73]. Lack of dyspnoea despite of low arterial oxygen level is named "silent hypoxia" [74].

The problem lies in the fact that dyspnoea is a subjective perception that is not related only to hypoxemia, but as well to breathing effort, hypercapnia, and pathologic affections in lung tissue [75]. Signals about these factors are transferred to brain stem and further to brain cortex.

Banzett reports that pain and dyspnoea are both processed in part by the limbic system. These symptoms alert the body to threatening conditions and the potential loss of homeostasis, motivating the subject to seek help and engage in adaptive behaviour [76]. Parshall has hypothesized that there may be a common central nervous system pathway involved in the perception of dyspnoea, irrespective of the underlying cause [77].

There are different pathways that enable the transfer of threatening signals to brainstem structures. Signals about low arterial oxygen level comes from carotid glomus through glossopharyngeal nerves, signals about high CO2 levels – from central chemoreceptors on the ventral surface of medulla oblongata, signals about breathing muscles effort – from proprioceptors of diaphragm, but signals from lungs – through the vagal nerve. Lung receptors that transmit wide range of mechanical and chemical stimuli, connected with lung damage are presented as free nerve endings of unmyelinated C-fibres and small-diameter myelinated Aδ-fibres. Signals converge at the nucleus of the tractus solitarius, and further to the somatosensory cortex and other regions of the brain involved in the interpretation of signals generating a perception of breathlessness [78].

The mechanism how SARS-CoV-2 virus induces the "silent hypoxia" is not quite clear. Li et al. have suggested that SARS-CoV-2 may affect the brainstem and the medullary cardiorespiratory centre of infected patients [79]. Others have suggested that the lack of breathlessness develop due to altered input from mechanoreceptors of the respiratory tract and chest wall [75]. It has also been hypothesized that SARS-CoV-2 impedes mechanical and chemical receptors on the vagal nerve, generally responsible for the exacerbation of dyspnoea [80].

In early stages of COVID-19 pneumonia when part of alveoli is collapsed, dyspnoea develops due to intrapulmonary blood shunting that occur due to loss of hypoxic vasoconstriction. As the lung compliance at this stage is high and CO2 level is normal, the main cause of dyspnoea is hypoxemia. However, hypoxemia is a weak cause of breathlessness and perception of dyspnoea may be low as has also been reported in other diseases with intrapulmonary shunting [75].

As interstitial oedema progresses, lung mass and elastance increases, work of breathing grows, and it increases the load to breathing muscles that in turn manifests as a shortness of breath [80],

Development of diffuse alveolar damage (DAD) affects the diffusion of breathing gases. Along with hypoxemia it leads to hypercarbia that is strong factor giving the sense of breathlessness [81].

Guan et al.found a level of dyspnoea as low as 18.6% in a retrospective data analysis of 1,099 patients, despite 86% having abnormal CT scans and low PaO_2/FiO_2 ratios. Other case studies have shown that the so-called "silent hypoxemia" was observed even in patients with elevated $PaCO_2$ which, combined with a low PaO_2, should induce dyspnoea [82]

As follows from mentioned studies the cause of dyspnoea is different in each patient's case and depends on the stage of disease, severity of the process and involvement of particular pathogenetic mechanisms occurring both in lungs and another organ systems.

Conclusions

Lung epithelium express ACE2 receptors that are binding sites for SARS-CoV-2 viruses. The highest density of receptors is found on the epithelial cells of upper airways, club cells of bronchioles and second type alveolocytes, loss of ACE2 molecules as the result of virus binding decreases the production of AT1-9 and AT1-7 changing the tissue reaction from anti-inflammatory to proinflammatory. This manifests with increase of pulmonary vascular permeability resulting in parenchymal oedema. Overfilled pulmonary capillaries and oedema compresses small membranous bronchi leading to areas of atelectasis that in turn affects ventilation/perfusion proportion in favour of perfusion. As under the influence of proinflammatory mediators the hypoxic pulmonary vasoconstriction is supressed, blood shunting through atelectatic regions takes place inducing arterial

hypoxemia, which is one of the main factors responsible for dyspnoea.

Proliferative phase of inflammation starts with proliferation of 2nd type alveolocytes basal and club cells of airways. Airways epithelial cells ingrow into alveoli that is termed bronchiolization, occlude them affecting gas diffusion and elimination of carbon dioxide. Hypercarbia is strong causative factor of dyspnoea. Proliferation of epithelial cells in bronchiolo-alveolar area is followed by epithelial-to-mesenchymal transition that initiates post-covid lung fibrosis. The pathogenesis of this process is less understood and future research in this field is necessary to elaborate new methods for prevention and treatment of post-covid lung affections.

Declarations

Authors have no competing interests that might be perceived to influence the results and/or discussion reported in this paper.

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