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Short Review

The Pores of Kohn, an Overlooked Pulmonary Structure: A Review

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Abstract

Many studies from the early 20th century on the significance of the pores of Kohn were assessed based on the pathogenesis and pathology of pneumococci pneumonia occurring in man. The pneumococci were carried in the edema fluid directly from alveolus to alveolus through the pores of Kohn and from bronchiole to bronchiole as a result of repeated aspirations, aided by breathing, coughing, and gravity. With the emerging minimally invasive and non-invasive techniques experimentations and the current medications; tackling exacerbations and improving the pulmonary function in various lung diseases remains a dilemma for clinicians and researchers. In this article, we aim to review specifically the pores of Kohn as this is the portal for the spread of infection but also lung recruitment during breathing.

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Keywords: Pores of Khon; Collateral ventilation; Pneumonia; Lung; Channels of Lambert

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Abbreviations

AM: Alveolar Macrophages; BLVR: Bronchoscopic Lung Volume Reduction; CO_2: Carbon Dioxide; ELVR: Endoscopic Lung Volume Reduction; FDA: Food and Drug Administration; HE: Hematoxylin and Eosin; ICU: Intensive Care Unit; NICU: Neonatal Intensive Care Unit; PK: Pores of Kohn; PMN: Polymorphonuclear Leukocytes; TEM: Transmission Electron Microscopy; 3D: Three Dimensional; µm: Micrometer;

Introduction

Small interalveolar holes within the lung are called pores of Kohn and knowing about these is very essential for routine clinical practice because tissue destruction in emphysema enlarges those pores. Many pulmonary diseases could affect the respiratory system in a large molecular array of antigen-antibody interactions at the various parts of the tract. This review paper solely discussed the alveolar pores of Kohn (PK). Considering the fact that many studies focused on morphologic and physiologic modalities on airspace characteristics, more correlations, specific differences, and limitations should be laid down between experimental animal models and human diseases using qualitative tissue processing and quantitative stereology methods [1]. However, due to the lack of in vivo methods, the role of PK in the mammalian lung is still not fully understood and the supporting experimental evidence and its partially contradicting hypotheses remain to be investigated [2].

Human data and basic functions of PK

The pores of Kohn (PK) are channels between two adjacent alveoli [3-5], or channels between lobes of the lung particularly in the presence of incomplete interlobar fissures [6]. The aperture between lobules is however known as the channels of Lambert [5]. The PK edges are composed of the intact alveolar wall [7] and are connective tissues that prevent lung collapse [6], and if underdeveloped could in children; lead to round pneumonia [clinically a lower respiratory tract dysfunction (dyspnea, cough, fever, and acute chest pain) with an associated radiographic opacity] with absence of channels of Lambert [8] because these discrete holes and accessory connections in the walls of adjacent alveoli are absent in human newborns but they develop at age 3 to 4 years [9,10].

The PK is thought of as fluid-filled connections between alveoli [3] and in case of airways obstructions (eg asthma), the potential bypass pathways are Lambert's broncho-alveolar channels (25 µm in diameter), or Martin's interbronchiolar or interductal communications (≈120 µm in diameter), but most of the collateral ventilation take place via the interalveolar pores of Kohn (≈5-10 µm in diameter) which are the most numerous [11].

While community-acquired Klebsiella pneumonia similar to pneumococcal pneumonia presents as a lobar pneumonia with visible air consolidation in the periphery of the lung adjacent to the visceral pleura, such condition spreads centripetally via interalveolar PK and may lead to lobar expansion [12]. The PK providing collateral ventilation [13,14] helps prevent excessive localized alveolar pressure, although they also favor the pneumococci spread as a result of the direct gravity-affected interlobar or interalveolar flow during

breathing and coughing [15]; thus the PK serves as portals for bacterial [16] and macrophage movements between alveoli; or in case of sequestrations which typically appear solid or cystic, PK may render intralobar sequestrations aerated and the communication with the contiguous normal lobe via the PK probably explains the frequency of infection in intralobar sequestrations [17].

PK are potential surfactant reservoir [18] and gets eroded during the development of emphysema [19,20], which can generate aerosols of surfactant film constituents due to increased lung tissue surface area [21-23]. An increase in PK decreases the gas exchange area, capillary bed, and elastic recoil, which in return can increase physical vulnerability to maintain lung architecture. However, ruptured alveoli walls are called fenestrae [24] and in conditions like esquamative interstitial pneumonitis, the septal thickening of the alveoli is an apparent decrease in the number of PK [25]. The establishment of improved oxygen delivery in patients with acute lung injury or adult respiratory distress syndrome is reached by mobilizing the patient's lung at close to total lung capacity, virtually eliminating the need for neuromuscular blockade - reducing the need for pressor support and sedation; aided by optimal recruitment of alveolar units achieved by developing intrinsic positive end-expiratory pressure with a short release phase, as well as through the principle of alveolar interdependency utilizing the PK [26].

Origin of the name pores of Kohn

PK was called "Pores of Kohn or Kohn pores" in 1894 ie at the end of the 19th century by Kohn's teacher Hauser, during a case presentation, in honor of one of this first scientists, a German physician, and pathologist Hans Nathan Kohn (1866–1935) who described them from his findings in a patient who had died of acute fibrinous pneumonia [27]. However, Cordingly [7] quoted many other studies describing the communications between alveoli since 1855 by Rainey, 1862 by Zenker; then Luschka (1863), Delafield (1882), Roosevelt (1890), Hansemann (1895), Schulze (1906), Laguesse (1912) and Marchand (1912) who observed bridges between adjacent alveoli in casts. The importance of collateral ventilation was ignored for over a century, but now, with their role in endoscopic lung volume reduction (ELVR) and the development of new bronchoscopic techniques, the study of these little channels has gained enormously in importance [28]. However, in the living, the PK was described not to function as channels for collateral ventilation but rather as a pathway for alveolar lining fluid, surfactant components, and cells like macrophages between the adjacent alveoli. So, the respiratory bronchioles (or alveolar ducts or Lambert channels) could most likely be responsible for collateral ventilation, and that represents epithelium-lined tubular communications between distal bronchioles and the adjacent alveoli. These channels were described by Lambert in 1955. The other channels that are responsible for collateral ventilation are the pathways that Martin explored in 1966. These pathways are accessory communications between terminal bronchioles from adjacent lung segments. Thus, bronchioloalveolar as well as interbronchiolar channels are considered to allow collateral respiration [29].

PK structure and specific function

Merkel (1902) raised a point that was supported by Marchand (1912), and other authors cited by Al-Tikriti [30] that; the PK frequency, size, and shape [31] - being round or oval, varied with the degree of lung expansion in different species and that they were in rats and birds, absent at birth and at the intersegmental septum [32,33]; but after the age of 1 month to 10 years [34] the PK arise as a natural consequence of aging. Other authors reported that the pores do not increase in number after the first year of life [35] and that the alveolar development is largely postnatal [36]. Secondary septa of variable heights subdivided the saccule into immature shallow alveoli, which in the rhesus monkey this process of alveolisation commences at 95 days of gestational age [30]. The PK has the ability to resorb trapped air [37,38] and is not associated with Marfan syndrome [39]. SEM stays appropriate to study the microanatomy of the pulmonary tissue because of its (i) high-resolution with 3-D views of the lung parenchyma, and (ii) it can be coupled with X-ray microanalysis which provides in situ elemental detection of the terminal bronchioles, alveolar ducts and sacs [35]; structures which mostly favor more the inspiration process [40].

The role of PK in different pathological conditions

Thomas [41] interpreted the restrictive pattern in two patients with asthma as a consequence of prolonged mucoid impaction of peripheral bronchioles that closed them completely up so that the initially trapped air had been resorbed by the PK. Yoshikawa, et al. [4] cited, that in cases with emphysema, there is a significant increase in PK (not confusing with fenestrae) which are pathways for collateral ventilation between two adjacent alveoli; and this decreases the gas exchange area, capillary bed, and elastic recoil [6,42,43], therefore increasing physical vulnerability to maintain lung architecture.

They concluded that based on the 3D characteristics of alveolar structure, breakdown of the lung framework changes the pulmonary function, and an increase in PK is associated with a decrease in a diffusing capacity with/without emphysema although these associations with pathological or radiological emphysema were not high. However, in round pneumonia, the associated radiographic mass appearance is believed to be caused by underdeveloped PK, with the absence of canals of Lambert limiting the spread of infection [10]. However, PK is currently thought of as fluid-filled connections between alveoli and only as collateral ventilation under extreme conditions of alveolar duct or terminal bronchiole blockage [42].

Nonetheless, Chronic Obstructive Pulmonary Disease (COPD) is characterized by the destruction of alveolar airspaces caused by an inflammation-induced imbalance between protease and antiprotease activity within the lung [43].

Macrophages movement

Cells like the Alveolar Macrophages (AM), vital in the removal of inhaled particles in the lung acini, and most of them presenting intracellular inclusions of calcium tungstate identified by the BEI mode of SEM, do pass through the PK [35,44] at a typical speed of 4μm/min^{-1} [45]. Since dilatation and air exchange take place at the level of the PK, the particle-carrying phagocytes were now predominantly located in the alveolar ducts and sacs rather than in the terminal bronchioles [35].

Asthma attacks are better understood in various weather conditions by gradual particle deposits and the detection of inflammatory macrophages at interalveolar pores connecting adjacent alveolar sacs. At days 1 to 3, the particle-laden phagocytes were predominantly located near the terminal bronchioles. This initial location of intracellular tungsten resembles the one that was previously reported in rats submitted to the inhalation of silica or iron carbonyl particles. At days 7-14, the tungsten-positive macrophages were detected mostly in the alveolar ducts and sacs [35], and a substantial development of the interalveolar pores on days 14 and 21 which coincides with septal rearrangement as secondary interalveolar septa become lengthened and thinner [44]. The addition of pores decreased the system elasticity in proportion to the pore area fraction (i.e. greater decrease as more of the septal wall features pores) [31].

Kikuchi, et al. [46] cited that major pathways for collateral ventilation still remain uncertain; however, collateral channels have recently been shown to be influenced by bronchoactive chemicals (eg: histamine, isoproterenol) and inferred to be a kind of small airway having smooth muscles but, are not PK. Thus, the PK would contribute to the rapid dissemination of inhaled particles (e.g. microbes) inside the deep lung tissue, even after these particles have been ingested by the polymorphonuclear granulocytes [47] and resident phagocytes [35]. The latter are the pulmonary alveolar macrophages, considered to have an essential but minor role in alveolar clearance as their number increases after inhalation of particles [2,47].

In conditions like congenital bronchial atresia, hyperinflation is thought to occur by collateral intersegmental air drift via the PK or via the bronchoalveolar, and interbronchiolar channels [48,49]. There is also a relationship between alveolar macrophages, septal gaps, and type-II cells. The type-II cells being the progenitor of the type-I cells [50], play a role in alveolar septal repair which goes beyond that of merely replacing injured or killed type-I cells, or secreting surfactant. Cytoplasmic flaps of type-I epithelial cells can cross the septum where some small type-I epithelial cell patches appear around the PK, evidently protruding from the other side [51]. Previous studies showed the estimate of the number of alveoli per human lung to 4.8×10^8 and the number of PK per alveolus is 24 [2]. In their study, Marco *et al.* concluded that the lung is an organ, that is constantly confronted with various pathogens simultaneously, implying that the alveolar macrophages availability is a crucial factor for a fast response of the immune defense through the regulatory PK that opens and closes due to pressure changes at the typical human breathing frequency of 12 to 18 min^{-1} [52].

Histological findings

HE staining of the normal alveolar structure revealed a few PK of about 10 to 20 μm in diameter on the alveolar walls, edged by relatively thick membranes, but was not directly rimmed by capillaries and are not identifiable of Silva impregnation staining and immunostaining for CD34 or immune staining anti-TF antibody [24]. Uncertainties are raised by the fact that the human lung is thwarted by the difficulties of securing specimens adequately fixed for electron microscopy [51]. The pore size notably affects the deposition pattern of inhaled nanoparticles but exerts a low impact on the total deposition fractions and the rhythmic alveolar wall motion is indispensable for inhaled nanomedicine to deposit in the distal alveoli [32].

The collapse of PK is age-dependent [53]; PK counts are increased with age, however, lung growth accompanying experimental pneumonectomy is not compromised by exposure to ozone (O3) a natural urban air pollutant [54]. PK also increases in chronic bronchitis or in asymptomatic asthmatics [55]. Although PMN, fibrines, fibronectins, and migrating fibroblasts, could be found in the alveoli, their development is favored by the PK in bronchiolitis obliterans or organizing pneumonia (intra-alveolar fibrosis), indicating a typical “butterfly” aspect [56,57].

PK functions and drug effects

Emerging technologies in 3D bioprinting and lung-on-a-chip models provide opportunities to study the effects of pharmacological interventions on alveolar microarchitecture. Also, lung tissues maintained in culture can be used to study the impact of drugs on alveolar wall integrity. These systems can replicate the alveolar environment, allow for controlled administration of drugs and the function of the PK can be studied under various conditions like airflow changes or drug exposures [58,59].

Experimental data

In Wister rats, during early lung development, the PK was demonstrated to serve as alveolar macrophage passageways [44]. In dogs, collateral channels behave like small airways that constrict under the influence of low CO_2, histamine,

or high airflow [5], even though the collateral resistance is highly lung volume dependent [60]. The PK would therefore be stretched dynamically as lung volume or transpulmonary pressure increased, but this change in dimension of the PK was not related to the cube root of lung volume [61]. The PK was also found in alveolar walls in camel that were similar to other mammalian species [62] but were found to be small and extremely rare in bovine lungs [63]. Therefore, the quantification of the PK in various species showed great variation according to the fixation technique, animal age, and site to alveoli in the lung and lobules with their size varying between 0.8μm to 15μm [20].

Current progress in PK analysis

Recent advances in technology allow three-dimensional (3D) analysis using a laser confocal microscope and a light microscope [4,24], or digital reconstruction of pathological images [4], or by physiological testing using an endobronchial in vivo measurement system called "Chartis" (Pulmonx Inc, Redwood City, CA, USA) along with Zephyr Valve system or Spiration Valve System, or by anatomical analysis of lung fissure integrity from Quantitative computed tomography (QCT) scans [28,43]. CT imaging could also be used to determine fissure integrity, degree of emphysema, and lobar volume to help with target lobe selection in patients eligible for bronchoscopic lung volume reduction (BLVR). Other techniques like endobronchial valve for BLVR (United States FDA approved), endobronchial coils, thermal vapor ablation, airway bypass stents, targeted lung denervation, bronchial rheoplasty, and biologic lung volume reduction (sealants and sclerosants), stand as a standard medical therapy in patients with severe emphysema [29,43].

Conclusion

There are numerous and frequent anatomical variations of the central airways making the examination unique for every individual. While technology continues to evolve and patient disease conditions undergo various classifications for the implementation of a specific treatment procedure, there is therefore need for further investigations about the PK in order for clinicians to avoid over-saturation of patients with oxygen masks, and indirectly, to avoid complicated outcomes.

Recommendation

Today's advanced technology should therefore be used to throw light into the central lung structure for better clinical acumen and a better understanding of respiratory diseases and monitoring of ICU and NICU patients.

Authorship

F.M. and A.K contributed to the content of this manuscript and to the approval of the final version to be published.

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