the aetiology and pathogenesis of emphysema

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The term "emphysema" was coined by Theophile Laennec in 1819 to describe what we today call "Surgical Emphysema". Surgical or Interlobular Emphysema occur when the pressure gradient between the alveolar lumen and the surrounding interstitium is exceeded. The tolerable limit to the steepness of the pressure gradient is 20-30cm. of water in neonates (1) and over 150cm. in adults. High intra-alveolar pressures are generated by (a) the use of violent artificial respiration in the resuscitation of neonates or of intermittent positive pressure respiration (e.g. following electrocution or drowning) (1a) (b) severe asthma, childbirth and strenuous exercise (c) violent coughing (e.g. in whooping cough), explosions or sudden decompression (e.g. in aircraft accidents and submarine escape training) (2) (d) traumatic rupture of alveolar walls when the lung is punctured by fractured ribs, a needle exploring the chest or penetrating objects (3). This type of "emphysema" implies air suction into the tissue planes (e.g. leakages from sutures in a bronchus or from a drain-tube) or a distension of interlobular septa and perivascular sheaths. Since 1819, the term "emphysema" has been corrupted to such an extent that it now relates to changes inside the lobule Laennec's Surgical Emphysema is not included in our definition.

In 1958 the Ciba Guest Symposium defined "emphysema" as "a condition of the lung characterized by an increase beyond the normal in the size of air spaces distal to the terminal bronchiole either from dilatation or from destruction of their walls". Since then the World Health Organization (1961) have excluded 'dilatation' from their definition and in 1982 the American Thoracic Society went even further by defining "over-inflation" as "an increase beyond the normal in the size of air spaces distal to the terminal non-respiratory bronchiole without destructive changes in the alveolar walls" thus separating emphysema from inflation.

The main difficulty in adopting these newer definitions lies in the distinction between pulmonary over-inflation and emphysema, e.g. persistent dilatation of an area of lung which is intrinsically weak will lead to severe emphysematous destruction. One cannot say for sure at what point the mildest amount of destruction can be recognized e.g. lesions may be basically distensive when they are actually the result of very fine destruction which weakens the walls of air spaces so that they distend abnormally with normal pressures. For this reason, the general consensus of opinion is that we should include 'over-inflation' as a Mild or Grade I type of emphysema. Indeed, though 'over-inflation' is primarily reversible, prolonged dilatation may lead to irreversible destruction. For the purpose of this paper I have adopted the 1958 Ciba definition of emphysema because though more recent definitions are more precise they have the shortcoming of being impracticable.

The classification of emphysema is based on the structural changes in the Secondary Lobule of Miller. The lobule, which is 1-2cm. in diameter, is the fundamental anatomical lung unit. It is roughly pyramidal and demarcated by a thin, fibrous membrane more highly developed in the upper lung fields. At the centre of the lobule are 5-10 terminal bronchioles, 1mm. in diameter, with no cartilage or submucosal glands and no air sacs or alveoli. The terminal non-respiratory bronchioles divide into 3 orders of respiratory bronchiole. The 3rd. order respiratory bronchioles open into alveolar ducts whose walls are virtually non-existent except for some smooth muscle strands. The wall of the alveolar duct is covered with outpouching alveoli which are in contiguity with the pulmonary capillaries so that they form a gas-exchanging unit. The alveoli are situated peripherally in the lobule. The alveolar duct musculature constricts in response to a depression in airway pCO2 so that inspired air is deflected from poorly perfused alveoli to lung areas with a more adequate blood flow. The respiratory bronchioles are situated at the centre of the lobule while the alveolar ducts and sacs are arranged in the peripheral zone.

On the basis of the arrangement of structures within the lobule pulmonary emphysema can be classified into:

- PARTIAL LOBULAR
- CENTRILOBULAR (including focal dust emphysema)
- PARASEPTAL
- PANLOBULAR
- IRREGULAR (related to scars).

Panlobular and Centrilobular emphysema can be divided further into (a) Mild, when there is pulmonary over-inflation (and, probably, the early stages of destruction). (b) Severe (4), when there is a recognisable pathological change in the structure of air spaces distal to the terminal bronchiole.

In Panlobular emphysema the entire lobule is affected whereas in Partial Lobular emphysema changes are localized either to the centre of the lobule (Centrilobular emphysema) or to emphysematous near scars (Irregular emphysema).

Bullae are dilatations of air spaces over 1cm. diameter associated with very severe panlobular emphysema (5).
Blebs are collections of air or gas in the sub-pleural connection tissue of the lung resulting from rupture of the pulmonary alveoli immediately beneath the pleura (6).

Severity of the emphysematous process is classified as follows:

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<th>Grade</th>
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<td>Air spaces are so small that they cannot be distinguished clearly without magnification. There is no retraction.</td>
<td>Air spaces are a little bigger than 1 mm. but architecture is still intact. Retraction is slight.</td>
<td>Air spaces are 'holes' larger than 5 mm. diameter which may be confluent and extend through the whole thickness of a 1 cm. lung slice.</td>
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Emphysema is more common in men than in women and the Centrilobular form is 20 times more common than the Panlobular type (7). Emphysema causes disability or death in about 3% of all patients at post-mortem (8).

Pathogenesis

The internal surface of an emphysematous lung is reduced although the total volume may be unchanged, increased or reduced. Since inspiration is a more powerful force than expiration, in emphysema air-trapping (9) occurs from obstruction to the emptying of intra-alveolar air. Inspiration is accompanied by dilation and shortening of the large and small air passages as far distally as the bronchioles and alveolar ducts. Emptying of the lung is brought about by the elastic recoil of alveolar walls and the contraction of muscle fibres in the alveolar ducts, the surface tension having been reduced by alveolar surfactant (10). If small bronchi are obstructed air reaches the lung tissue distal to the obstruction through pores of Kohn from adjacent portions of lung whose air supply is unimpeded (11). Young children possess a few, ill-developed pores of Kohn but with increasing age the pores become larger and more numerous and collateral ventilation assumes a greater importance.

The current hypotheses of the pathogenesis of emphysema are:

i. Chronic bronchiolitis causes temporary or permanent obliteration and destruction of respiratory bronchioles so that air passes by collateral ventilation into air passages distal to the obstruction and, as a consequence of prolonged 'air trapping' in the acinus, air passages beyond the mucous or mucopurulent obstruction are disrupted producing an 'air pool'. The pressure distal to a bronchial obstruction in the collaterally ventilated lung is raised during expiration especially in forced expiratory efforts, e.g. coughing, which may be sufficient either to drive out the obstructing mucous plug or, if bronchiolar obstruction is permanent, to disrupt the walls of the 'pool' and establish a free airway with neighbouring acini producing a 'common pool' (12). Chronic inflammatory damage to respiratory bronchiole walls leads to weakening of the second and third order respiratory bronchioles which subsequently dilate and break down so that the emphysema is primarily centrilobular (or sometimes, panlobular) in type (13). Contiguous alveolar tissue is also involved in the inflammatory process.

ii. Acute attacks of bronchiolitis cause:
   a. narrowing of the terminal and respiratory bronchioles which impedes normal expiration,
   b. collapse of air passages due to a loss of the extra-mural attachments supporting alveolar walls (15),
   c. extensive atrophy of the walls of medium-sized bronchi due to a loss of bronchial cartilage and muscle and peribronchial connective tissue.

Damage to lung parenchyma occurs. If, for example, the peribronchial connective tissue is lost the bronchioles will collapse in expiration (16).

iii. Ischaemic changes in the bronchi and peripheral parts of the lung, e.g. alveolar walls, can occur because of:
   a. occlusion of bronchial arteries (17),
   b. ischaemic obliteration of alveolar capillaries,
   c. bronchopulmonary anastomoses which develop when ischaemia occurs and which can lead to secondary haemodynamic changes in the pulmonary circulation and produce a decrease in the blood supply to the lung parenchyma (8).

iv. Peribronchial coal-dust deposits weaken the muscle fibres in the walls of respiratory bronchioles and destroy the peribronchial alveoli.

v. Traction exerted by respiratory movements causes damage to the distal respiratory bronchioles (19). Actually, traction by itself will only cause over-inflation but if it is associated with, say, bronchiolitis the change can become irreversible.
Aetiology:

i. Congenital:
   a. Congenital defects in a bronchus lead to air-trapping during expiration and consequent overdistension in the zone supplied by that bronchus.
   b. Congenitally maldeveloped alveolar walls may undergo premature degeneration or may fail to develop properly.
   c. Familial emphysema may be associated with
      i. homozygous autosomal recessive serum 2 — antitryptsin deficiency
      ii. familial mucoviscidosis. Fibrocystic disease may be significant in the production of emphysema but usually results in bronchiectasis and diffuse interstitial fibrosis.
   d. Abnormalities of smooth muscle, elastin and collagen associated with emphysema are being investigated.

ii. Experimentally, emphysema can be simulated by producing an acute bronchiolo-alveolitis (using nitric acid or papain) but rarely occurred following bronchiolar scarring from acute bronchiolitis or fibrogenic dust foci (using silica, asbestos and road dust) and was never associated with non-fibrogenic dust foci (produced by using perpex, fibreglass, wood or carbon dust).

iii. Inhaled chemical substances, e.g. cadmium fumes in anticorrosion coatings.

iv. Distensive forces (e.g. severe asthma and blowing wind instruments) combined with chronic inflammation.

v. Ischaemia due to pulmonary and bronchial artery obstruction.

PANLOBULAR EMPHYSEMA

"A lobular emphysema which involves all air spaces beyond the terminal bronchiole more or less evenly."

It is a common form of emphysema and is of the destructive type in 78% of cases. It may occur in any part of the lung, but there is a tendency for it to occur more frequently anteriorly, i.e. in the lingula, middle lobe and anterior basal segment of the lower lobe. The normal alveolar diameter of 0.1 mm. increases with age to 0.2 mm at 30 years but remains the same in later years. The average diameter of respiratory bronchioles and alveolar ducts increases from 0.2 mm. to 20 years to a maximum of 0.7 mm.

In mild panlobular emphysema the spaces are abnormally large holes of 1.0 mm. or more in diameter scattered throughout the lobule. The respiratory bronchioles and alveolar ducts enlarge by stretching, and the cup-shaped alveoli become shallower (i.e. saucer-shaped). In moderate panlobular emphysema there is partial destruction or atrophy of fine respiratory tissue and the number of intact alveolar walls is reduced. The small (5-10 micron diameter) pores of Kohn become large, perforated, cribiform fenestrae. In several panlobular emphysema there is complete destruction of respiratory tissue. Since pulmonary arteries and arterioles are more resistant than other structures, some branches of the pulmonary arterial tree will remain patent.

Environmental and racial factors must be taken into consideration in reviewing the regional distribution of panlobular emphysema. It is more common in the tropics than in temperate climates and more severe in the U.K. than in other countries especially S. America and Africa. Though age may not be important in aetiology the lesions increase in severity through the years possibly because there is more time for harmful agents to act on the lung. Mild panlobular emphysema in old people is as common in men as it is in women but when it is coexistent with centrilobular emphysema it may be associated with cigarette smoking and chronic bronchitis and is therefore more common in males.

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CENTRILOBULAR EMPHYSEMA

"Emphysema of the centre of the lobe from involvement of respiratory bronchioles."

It can be (a) mild, when the air spaces appear enlarged but there is little destruction of the alveolar wall, or (b) severe, when the pulmonary vessel remnants are all that is left to indicate alveolar wall destruction.

Gough prefers to reserve the term 'centrilobular emphysema' for a condition associated with histological evidence of bronchiolitis. Mild centrilobular emphysema is common especially in people exposed to coal-dust-, haematite-, graphite-, laden atmospheres. In these cases, however, there is no evidence of bronchiolitis and some prefer to call it 'dust retention' and include it with the pneumoconioses. Pneumoconiosis is a comprehensive term covering a group of dust diseases defined in the N.I. (Industrial Injuries) Act of U.K. as 'fibrosis of the lungs due to silica dust, asbestos dust or other dust and includes the condition known as dust retention'. The lesions in this mild type of emphysema are darkly pigmented clusters of dilated respiratory bronchioles surrounded by dust cells which may become incorporated within the wall and entombed by the alveolar lining cells. Though centrilobular emphysema does occur in some coal workers, destructive centrilobular emphysema is not characteristic of coal-dust exposure. In severe destructive centrilobular emphysema the lesions are more than 1 mm. diameter and remnants of the arteries and arterioles cross the emphysematous spaces. Small, rounded, calcified nodules (? healed tuberculous lesions) are sometimes found attached to these strands especially at the apex of the lung. Lesions are usually large at the apex and small at the base. This is attributed to either the differences in pressure, or poor circulation in the upper lobe. The emphysematous spaces are modified proximal respiratory bronchioles and terminal non-respiratory bronchioles.
Aetiology:

Common all over the world possibly due to a universally distributed agent, e.g. cigarette smoke or a virus. It is more common in males and only rarely occurs in non-smokers.

i. Coal-dust, graphite and haematite cause dis­tensive 'focal' emphysema but together they account for a very small percentage of cases and there is never an associated bronchio­ritis. The dust is carried to the lobule centre where it accumulates and weakens the respira­tory bronchiole walls. The dilation is maintained by:

a. traction of pulmonary elastic tissues on the airways (37),
b. inspiratory force required to expand pigment-laden macrophages (38),
c. shrinkage of masses of pigment-laden macrophages (38).

ii. Irritant gases absorbed by carbon particles may cause mild emphysema.

iii. Disruption of bronchiolar clearance mecha­nisms at the lobule centre (39) by:

a. inflammation due to H. influenzae, Str. pneumoniae and viral infections.
b. chemical inflammation especially cigarette smoke, smoking habits and central­lobular emphysema being closely re­lated.

iv. Mechanical overinflation associated with other causes will produce permanent destruction of airways and is responsible for the balloon-like appearance of the lesions and the relationship between the size and vertical position of the punched-out spaces at the centre of the lobule.

v. Gaseous irritants commonly encountered in industrial regions, e.g. sulphur dioxide, ozone, oxides of nitrogen, phosgene, nitric acid and papain, damage the lobule centres possibly due to the pneumonia finding a 'locus minoris resistentiae'). Cigarette smoke, ozone, aluminium oxide particles and sulphur dioxide reduce the surface tension of elastic recoil permitting over-inflation and tissue disruption.

PARASEPTAL EMPHYSEMA

"Emphysema adjacent to the septa from involvement of the alveolar ducts and alveolar sacs".

The lesions are often pigmented and remnants of the pulmonary venules pass out radially towards the septa. There are no intact alveolar ducts or sacs and spaces communicate with small air pasages at the lobule centre.

Aetiology:

Not certain, but probably due to a combination of injurious agents, mechanical factors (e.g. spontaneous pneumothorax, diaphragm's forceful action or the respiratory expanding force trying to overcome airways obstruction and, in the process, pulling degenerate lung parenchyma from its frame­work (4), and inflammation.

IRREGULAR EMPHYSEMA

"Irregular emphysematous involvement of the acinus adjacent to scars". It is also known as scar or paracicatricial emphysema.

Aetiology:

This type of emphysema is seen in relation to scarring, e.g. old, healed tuberculous lesions. The bullae can rupture (especially in the young) producing spontaneous pneumothorax.

"Since the days of Laennec and Baillie work on emphysema has come a long way. Today, we have solved most of the problems regarding its nature but we are left with a mass of conflicting evidence from which we have to sort out the important from the irre­levant."

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