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COMMENTARY

Is the Primary Mechanism Underlying COPD: Inflammation or Ischaemia?

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Abstract

The mechanisms underlying the majority of COPD cases have remained ill-defined. Cigarette smoke contains many toxic chemicals that certainly cause some inflammatory responses, but this article advances a hypothesis that the nicotine and similar compounds within the smoke acting as vasoconstrictors of bronchiolar arterioles may be more important via multiple small infarcts that eventually destroy lung tissue. The hypothesis can explain many of the known features of COPD and if accepted would significantly alter the approach to this condition.

Introduction

With the first national COPD guidelines, COPD became the unifying term to describe a group of airway conditions characterised by chronic airflow limitation (1). Recent reviews cite multiple mechanisms including inflammation, immunity, tissue repair and destruction (2, 3, 4). A few well documented processes cause specific subtypes of COPD, e.g., alpha-1-anti-trypsin deficiency.

Yet, for most COPD cases with either centri-lobular emphysema or small airway disease without radiological emphysema, this author has been skeptical of the progress in understanding COPD mechanisms. A recent observational report that statins may be the most effective drug for COPD (5) triggered an editorial in a primary care journal (6) in which I raised my doubts; this article enlarges on that comment to challenge conventional wisdom and suggest an alternative approach.

The hypothesis

Could a major subtype of COPD be due to vascular insufficiency of small airways resulting from inhaled vasoconstrictive agents, or be, in effect, "Buerger's Disease of the lung"? In other words: could the prime mechanism be bronchiolar arterial spasm leading to infarction of small bronchial arteries and thus destruction of centri-lobular lung tissues? It may be nicotine acting as a vasoconstrictor that is the active smoke moiety, rather than the inflammation caused by the chemicals in the tar.

What happens when a cigarette is smoked?

The cigarette is an extremely effective inhalational device. Tobacco burns at about 800°C, and as the particulate leaves the cigarette the mass mean diameter (MMD) is about 0.1 microns, i.e., an ultrafine particulate. As smoke cools

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and mixes with airway humidity, there is some aggregation, many of the chemicals transform into more stable chemical states, and some dissolve into water droplets. But the MMD remains about 1 μm, so smoke particles penetrate deep in the lung and in health most particles reach the alveoli. In obstructive airway disease, perhaps half reach the alveoli (7). The smaller particles remain in suspension in the airways/alveoli and are later exhaled. Much of the particulate burden deposits along the airway mucosa, where the chemicals (including many carcinogens) directly irritate and inflame. The response in the large airways with mucus gland hypertrophy and mucus production is well known, but "chronic bronchitis" of larger airways has only weak associations with functional decline. Toxic effects include loss of the ciliated cells and squamous stratification, but this, too, can occur without loss of function, i.e., it's a consequence of active smoking rather than the cause of the obstruction. And on smoking cessation, the ciliated epithelium can recover.

But then consider what the nicotine might do. Nicotine is unlikely to be in a gaseous phase at body temperature, and is likely to be within water droplets that are deposited along the bronchial tree. Nicotine is a known vasoconstrictor of cardiac and other vasculature at concentrations an order of magnitude lower than those likely to be present in the airways (8). Absorption of nicotine to reach the brain is largely via the alveoli into the pulmonary circulation to cause the cerebral high within a few seconds. Alveolar levels, presuming a diffusion gradient, must be higher than cerebral levels, and there must have been even higher concentrations of nicotine within the bronchioles supplying those alveoli. And as airway deposition is not uniform, peak concentrations are likely at airway bifurcations.

The bronchial arterial supplying the bronchioles is an end artery. As it branches into the lobules and sublobules each artery is said to be a plexus of vessels that can anastomose with each other and thus protect the bronchus, but in the very small airways the bronchial arteries must become fewer and thus be vulnerable. The most peripheral sections of the bronchial circulation drain into the pulmonary veins. The proportion of the bronchial blood flow draining into the pulmonary circulation varies with the respiratory cycle and is increased in pulmonary disease. Virchow, over a century ago, showed that reverse flow (i.e., pulmonary to bronchial) could "protect" the bronchi after ligation of the proximal bronchial artery (9). Such facts may have prevented further consideration of the vascular structure over the years.

Consider how a vasoconstrictor might affect this. Vasoconstriction could happen along the length of the bronchial artery, with potentially greatest effect peripherally, first because the vessels are smaller, and second, because the distances between airway and artery and the thickness of airway and arterial walls are less. If flow in a small bronchiolar artery were to slow or stop, then the tissues supplied would be at risk. The relative particulate deposition at the bifurcations within the upper lobes is higher per unit lung volume in the upper lobes (supported by experimental (10) and theoretical data (11), making it likely that tissue nicotine concentrations in the upper lobes are also greater. This parallels the apical predominance of damage.

The lobular structure means that the nearest systemic vessel will be in the centre of the next lobule, i.e., with alveolar space in between, so there can be no rescue from other systemic vessels. Unless there is communication with the pulmonary circulation to maintain the tissues (albeit with desaturated blood), there could be a micro infarct affecting that particular bronchiolar vessel's territory, i.e., the airway at the centre of the lobule.

The spasm may be temporary while peak nicotine levels are present and recover later so any collateral supply from the pulmonary circulation may only have to "tide the situation over" until the bronchiolar muscle relaxes and normal supply is resumed. And of course the alveoli at this stage would be unaffected. Old texts describe modified bronchial arteries or "sperrarterien," which have been considered to be abnormal sclerosed bronchial arteries (12).

However, for the low-pressure circulation to flow into these systemic arterioles, there must be a higher pressure in the pulmonary artery. West's 4 zones (13) describe less pulmonary blood flow per unit lung volume in the upper zones. Indeed West's zone 1 shows how at rest there may be no flow in the pulmonary circulation at the apices, as the pulmonary arterial pressure is less than the hydrostatic effect of being a biped. In such a situation there could be no "rescue" of tissues supplied by a bronchial artery in spasm.

If we presume that there are 12–25 airway divisions (less in central areas and more in peripheral), then there are a million of the smallest airways. If each cigarette were to damage just 2 or 3 of these small airways, then there would be loss of about 50% of the cross sectional area over 40 years. That is not to imply a loss of 50% in FEV_1 since the relationships between small and large airways are more complex, but it shows that sustained trivial amounts of damage would lead to significant losses. The damage to so few cells would not be noticeable by the smoker at the time.

The above is a simplification and has not attempted to factor in differential pressures in the respiratory cycle, the sympathetic/parasympathetic innervation, or the effect of high nicotine concentrations on these, but the simple premise of a primary vascular aetiology is enough for now.

How does this fit with other observations?

Sensitivity to nicotine

Nicotine and related compounds affect systemic arterial smooth muscle in laboratory studies at concentrations much lower than those likely to be prevalent within the

airway. The stimulus is from a cocktail of smoke products – nicotine is the one that is easily measured. There is strong evidence that arterial disease in the lower limbs is more likely in smokers and its most severe form is Buerger's Disease, in which young/middle aged adults develop severe arterial disease of their legs that can lead to amputation.

Only some smokers are affected, thus demonstrating a differential sensitivity to the chemical(s) and a similar variable host response might also be present in the lungs. So, any bronchial arterial damage may be dependent on both the exposure factors (how much is inhaled, how much deposited etc.), whether or not there is some collateral "rescue" from the lesser circulation, and on the host response.

Thus, for half the population to have vessels that are either not sensitive to the chemical challenge or, if so, have means of negating the effects is both plausible and testable.

Inflammation

The type of inflammation of COPD is dominated by CD8, rather than CD4 cells as in asthma, and shows little (if any) response to steroid anti-inflammatory therapy. Ischaemic cell death leads to a clearing up operation – a type of inflammation that is characterised by CD8 cells and the result in most tissues is usually to produce fibrotic tissue (14). Inflammation following cell death is unlikely to be steroid sensitive and nor to have any of the immunological properties that characterise asthma. But alveoli washings would reveal an increased cellular component and in particular one would expect neutrophils to be dominant. If the damage was to a few airways only, the "signal" from any washings would be difficult to interpret.

Inflammation has to resolve and often that is by fibrosis. Repeated insults in the central part of a lobule may therefore lead to some scar tissue, which may show up radiographically as a thickening in the centre of the lobule. But, scars in most tissues contract over time, becoming adherent to surrounding solid tissues. Scar tissue in the centre of a lobule has little to bind to. If the adventitial connections of surrounding alveoli are damaged, then the elasticity of the surrounding lung will "pull" those alveoli away from the area of infarction, so creating a space. In that space the fibrotic tissue would be "floating" and may well be resorbed leaving a hole – the centrilobular hole with some surviving alveoli around it. The bronchi supplying that area proximal to the infarct now have fewer elastic linkages with surrounding tissue, and thus there is an inability to prevent airway collapse during expiration. So, there are fewer small airways with reduced mechanical protection. Both lead to reduced capacity for expiratory air flow.

An alternative process by which airflow limitation could occur is to extrapolate from larger airways that have a damaged arterial supply eg the trachea post surgical resection. The damaged wall scars and shrinks, creating a stenosis. If this were replicated in small airways, it could this be a means to generate small airway disease without emphysema. This, too, could lead to increased radiographic markings at the centre of the lobule. Would this be identifiable under a microscope where the slicing and angulation in preparing the specimens does not make it easy to work out how the patterns have arisen? So far, no literature has been found to help decide.

The sequence of ischaemic damage, an inflammatory clear up process, and resolution with some fibrosis occurs in all tissues. The effects in the lung are likely to be different as the structure of a largely gas filled organ with two blood supplies is less predictable. But the variability could be such that some individuals avoid damage either by being insensitive to nicotine, or by having pulmonary collaterals, while others develop infarcts that lead to tissue resorption or airway stenoses.

Radiology

CT has improved the imaging of the lung, but it is difficult to infer from images how the changes happened. With this hypothesis, there will be fewer surviving airways ie with less cross sectional area and an altered mechanical structure such that there is less elastic tissue to hold airways open in expiration. The combination of fewer airways and less support would produce the "small airways disease" component that we may see separately from the emphysematous component. There may be a gradation of damage. The bronchiolar muscle layers could be picked off with some fibrotic tissue in the walls, or the airway as a whole could end up with a tubular stenosis.

Early pathology studies in the 1970s reported fewer small airways (15) and a more recent CT study of airways from Vancouver (16) found that the total number of small airways was reduced rather than that all airways were narrowed. Other radiology studies note that there is increased fibrosis detectable on the CT scans of smokers (17).

This is most marked in the centre of the lobules and could represent the resolving inflammation post ischeamia, and while individual lesions shrink (or are resorped) and thus become less obvious, they would be replaced by new lesions, as smoking continues. It is hard to determine causation from a static radiological image showing combinations of airways and tissues with various stages of damage, but finding significant fibrotic change is compatible with the hypothesis.

The mechanical effects in different parts of the lung will differ as few lungs are homogeneous. Scars from prior infections, local developmental defects, congenital lung cysts will make for variable flow pressure volume relationships. Gravity and relationship to septae will also have an effect. Paraseptal emphysema has never fitted with either inflammation hypotheses (inhaled particulates are not concentrated at the lung periphery) or to an enzyme deficiency, but mechanical factors could provide an explanation. The subpleural areas

are the furthest extremity from the blood supply, are perhaps the most prone to developmental failures, and the mechanical forces at the edge of the lung will differ from more central regions.

Pan lobular disease is probably an entirely separate entity, but smokers with alpha-1-anti-trypsin deficiency develop disease earlier in life, so it is possible that the combination of disease mechanisms is enhancing an effect whereby neighbouring areas of lung destruction co-alesce into larger spaces. The mechanisms may be mechanical as the surrounding lung's elastic properties, devoid of some attachments, lead to retraction. This is analogous to the way that giant bullae develop (18). Once there is mechanical distortion, the strain on individual elastic elements will be unequal and some may simply "snap" and as they do so the bulla will increase in size.

Other observations

- Low tar cigarettes: When the industry developed low tar /low nicotine cigarettes, the expected safety gains were not seen. It seems that addicted smokers inhaled more deeply to gain the cerebral high. Thus any vaso-constrictor problem would have been the same.
- Other inhaled agents: In the last 20 years, some patients present having inhaled or snorted addictive drugs with severe COPD at a relatively young age. The mix of drugs and the relative doses are variable but certainly cocaine is an extremely potent vaso-constrictor. There has been no obvious explanation postulated as to why they should be so severely affected and so much younger.

Effects of pharmacology on COPD

Although there is good evidence that current COPD drugs alter the exacerbation rate, sufficient to justify prescription, there is little effect on long-term decline, despite several large studies of steroids and bronchodilators. In contrast, smoking cessation, i.e., removal of the stimulus definitely reduces functional decline, oxygen (in the late stages) improves survival via effects on pulmonary hypertension.

So, a study reporting an apparent 25% improvement in mortality associated with statin use was a surprise (5). The study included all COPD hospital admissions in a single year across a country, and linked individuals to their GP drug prescriptions. Unadjusted outcomes of those prescribed or not prescribed statins were similar, but when control was added for known cardiac and other diseases, there was a 25% lower 3-year mortality in the statin-treated group. It is observational and the study methodology cannot prove causation. But to argue that this is purely statistical means arguing that a cohort with known heart disease, stroke and other problems would have the same outcome as a group without, which flies in the face of all known epidemiology.

Statins have no obvious effect on the airway – they do affect cholesterol/lipid metabolism, flow in blood vessels, and may help to prevent stasis and clotting. It is unlikely that the lipid effects are important within the lung but the claims for benefits on blood flow and clotting may be important. In the data from the National Audit of Myocardial Infarction Project that compared patients who were and were not prescribed statins after a heart attack, there were apparent differences in mortality within the first 60 days, i.e., far too early for any lipid deposition differences to be responsible (personal communication). Perhaps statins have a benefit in maintaining flow in these narrowed vessels. However, while mechanisms remain speculative, the differences in outcome certainly justify a randomised trial.

Occupational and environmental exposures

Dust exposures in coal mining and other occupations are claimed to cause COPD, and there are similar claims for small particulates and especially for the ultrafine particulates. Such reports do not fit with the vascular hypothesis in this article. So, if there are common mechanisms, either the vascular hypothesis advanced here is erroneous, or the epidemiology that underpins the environmental/occupational story needs re-examining.

A recent review of epidemiology methods (19) points out the difficulties in reaching causal statements from the many studies. Many are cross-sectional, few have all relevant exposures well documented, and few are large enough or complete enough. It is particularly difficult to control for confounding when smoking, ageing, cohort effects, and the environmental exposure are all affected by time. The Schwartz paper (19) points out how difficult it is to have confidence that all the appropriate controls have been fairly and evenly applied. It is difficult when reading papers to challenge the logic hidden within the statistical "black box."

Two illustrative cautions about coal dust:

a) The widely cited Rogan study (20) was cross-sectional and actually not statistically significant ($p = 0.06$) in the non-smokers. The internal controls for ageing, dust exposures, and smoking do not meet the Schwartz standards as smoking and the dust exposures were treated differently: smoking as a category (smoker, ex-smoker, non-smoker), dust as a continuous cumulative variable. And there was no control for cohort effects such that those born 30 years later were taller with larger lungs than their peers (21).
b) The mean *respirable* dust exposure of the face work miners above was 4–5 mg/m^3. Over an 8-hour day of moderate sustained exertion this translates to a daily intake of about 60 mg of dust. This is a lower total dust burden than from 3 average cigarettes of

the time. And cigarette dust contains many more active compounds than coal dust. Developing this further requires a more detailed paper–particularly if the vascular hypothesis gains credence.

Environmental/pollution dust exposures (as in PM10), are an order of magnitude less than in coal mines and there are no studies to show that severe COPD has resulted from PM10 alone. Exposures to indoor wood smoke in the third world has more plausibility and will include more active chemical agents. But all such studies have to address the Schwartz issues as cumulative exposure, age, other exposures (including cigarettes), and co-morbidity all increase with time.

None of the environmental or occupational studies compare with the 40-year observations started by Doll and Hill on a cohort of 40,000 doctors demonstrating that smoking 25 cigarettes a day equates to an increased COPD risk of about 20-fold (22). Not only was this longitudinal and commendably complete, but it produced answers that were of a magnitude such that statistics were hardly necessary.

Progression of disease

Continued smoking causes a progression of COPD with declining function and a shortened lifespan. If a person stops smoking then the Fletcher hypothesis was that they would all stop declining at an accelerated rate, but while some patients so stabilise on stopping smoking, there are exceptions. These exceptions do not fit the vascular hypothesis but possible explanations include:

- Airway damage/distortion such that impaired clearance of secretions/bacteria leads to recurrent infective exacerbations;
- Damaged arterioles are more prone to other arterial diseases, e.g., atheroma and thus continued loss;
- Arterioles that have survived courtesy of the pulmonary circulation but are chronically hypoxic. The effects of chronic hypoxia on a systemic vessel is unpredictable and so are the implications of a local right to left shunt, especially if replicated over many local areas.

Another observation is that patients with COPD desaturate on submaximal exercise of a 6-minute walk (23). If there was a matched loss of alveolar surface area and pulmonary circulation then desaturation would be expected toward maximal exertion. If the pulmonary artery and vein remain after the systemic supply to the bronchiole is removed, there would be a series of intrapulmonary shunts within the uppermost parts of the lungs (West zones 1 and 2). This would only become apparent on exertion as the pulmonary arterial pressure pushes blood toward the apices. Again, speculation, but an explanation that fits with the observed physiology.

Conclusions

The mechanisms of COPD have been elusive. Have we misdirected ourselves pursuing the inflammation story, and if so has that been to the misfortune of our patients? COPD is probably several disorders that are characterised by airflow limitation, and a vascular hypothesis could be one. If proven, then therapeutic approaches may change and the statin observation could be the start. So, the challenge is for others to prove this wrong – or not?

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Declaration of Interest Statement

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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