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Original Article

Decreased mucosal oxygen tension in the maxillary sinuses in patients with cystic fibrosis

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Abstract

Background: Pseudomonas aeruginosa in the sinuses plays a role in the lungs in cystic fibrosis (CF) patients, but little is known about the sinus environment where the bacteria adapt. Anoxic areas are found in the lower respiratory airways but it is unknown if the same conditions exist in the sinuses.
Methods: The oxygen tension (pO_2) was measured, using a novel *in vivo* method, in the maxillary sinus in a group of 20 CF patients.
Results: The CF patients had a significant lower pO_2 on the mucosa but not in the sinus lumen as compared with a control group of non-CF patients. Anoxic conditions were found in 7/39 (18%) of the sinuses from where we cultured *P. aeruginosa, Stenotrophomonas maltophilia* and/or coagulase negative staphylococci.
Conclusion: These findings support our hypothesis that *P. aeruginosa* can adapt or acclimate to the environment in the lungs, during growth in anoxic parts of the paranasal sinuses.

Keywords: Pseudomonas aeruginosa; Cystic fibrosis; Maxillary sinuses; Oxygen tension; Sinus surgery; Catheter optode

1. Background

Cystic fibrosis (CF) is a genetic disease caused by mutations in the gene for the CF transmembrane conductance regulator (CFTR) protein, resulting in altered chloride transport, in multiple organs, which comprises the mucociliary function and renders the mucus viscosity and the mucosa more susceptible to infections [1]. Nasal and sinus inflammation is a frequent condition in patients with CF, commonly leading to findings as congestion, mucopurulent material in the nose cavity, polyposis, abnormalities of the lateral nasal wall, mucoceles, and hypoplasia of the paranasal sinuses [2]. Such conditions might affect the O_2 exchange and the O_2 content in the sinuses and thus the microenvironment of its bacterial community.

The gas exchange in the maxillary sinus takes place via the ostium and the mucosa that absorbs and consumes O_2. The diffusion through the ostium obeys simple physical laws and depends on the patency of the ostium, the volume of the sinus and the respiratory work in the nose.

The absorption of O_2 from the sinuses as well as the change in the O_2 content in the paranasal sinuses after obstruction of the ostium, are thought to be important factors in the pathogenesis of sinusitis. There is a significant decrease in the luminal O_2 content in persons with acute sinusitis or allergic rhinitis compared with patients without symptoms [3,4]. Aust and Drettner [4] also found decreased O_2 tension (pO_2) in a group of patients

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with recurrent sinusitis and in a group of patients with obstructed ostia (all non-CF). They did not find pO_2 to be related to the presence or absence of antral pus or mucus. Carenfelt and Lundberg [5] reported a pO_2 close to zero in some purulent sinus secretions with *Streptococcus pneumoniae* or *Haemophilus influenza* compared with 96 mmHg in non-purulent secretions. They conclude that the gas composition in the sinuses influences the bacterial growth, as well as the bactericidal function of the granulocytes, and that the O_2 levels also might be of importance to the mucociliary activity. Purulent sinusitis should thus be treated by drainage of the sinus cavity, not only to reduce the debris, but also to improve the condition for the local host defense mechanisms of the sinus.

The limited research that has been published regarding pO_2 in the sinus deals with non-CF patients. CF patients have a different inflammatory response in their sinus mucosa as compared with non-CF related rhinosinusitis [6,7], and the O_2 conditions and their importance for rhinosinusitis in these patients are unknown. However, it has been shown that hypoxia contributes to a reduction of cell surface CFTR [8], which might have an additional negative impact in the sinuses of CF patients.

Chronic *Pseudomonas aeruginosa* lung infection develops in most patients with CF. Once the bacteria have established a chronic infection in the lungs, they cannot be eradicated. *P. aeruginosa* is a facultative anaerobe, which can proliferate and adapt to anaerobic environments, when thick layers of mucoid exopolysaccharide surround the bacteria (biofilm). Such biofilms are known to exist in the sinuses [6] and in the lungs, and the presence of such biofilms limit the diffusive supply of O_2 which then can lead to total O_2 depletion in the sputum [9]. In addition, numerous of polymorphonuclear leucocytes (PMNs) in the infected bronchi exhibit strong consumption of O_2 for production of reactive oxygen species (ROS) [9–13].

Under such anoxic conditions *P. aeruginosa* can achieve anaerobic growth either based on denitrification using nitrate as a terminal electron acceptor or by fermentation of arginine [9–12,14].

It has been indicated that *P. aeruginosa* responds to hypoxic mucus with an upregulation of alginate production, which may decrease the susceptibility to some antibiotics. Also, novel therapies for CF include removal of hypoxic mucus plaques and the use of antibiotics effective against *P. aeruginosa* adapted to anaerobic environments [10].

In the mucus with low pO_2, *P. aeruginosa* can make alterations due to mutations caused by the ROS or conversion in phenotype, e.g. becoming mucoid and developing antibiotic resistance, in order to adapt to different focal niches [15,16]. Studies of *P. aeruginosa* suggest a correlation between nutrient limitation, growth rates and conversion to mucoidy [17], and we speculate that the same applies for anoxic conditions.

The upper airways are shown to be a gateway for acquisition of opportunistic bacteria like *P. aeruginosa*, where the paranasal sinuses can act as a reservoir. Concordant genotypes have been found in the sinuses and in the lungs [18]. Our hypothesis is that *P. aeruginosa* adapts to the environment in the paranasal sinuses where some bacteria mutate or converse their phenotype [19]. This results in bacterial strains that are fit for spreading to the lungs, where they can maintain an ongoing deleterious infection.

Our present knowledge about *P. aeruginosa* is primarily related to the lungs. The pattern of inflammation differs in the sinus from the findings in the lower airway specimens of chronically infected patients with CF [20]. There is a Th2 dominated response in the lungs, while there is a significantly reduced PMN response in the sinuses, probably due to the higher concentration of IgA in the sinuses then in the lungs [21]. The latter statement combined with the fact that antibiotics more difficultly penetrates and achieves therapeutic levels in the sinus cavity than in the lungs, are some of the reasons why the immune response in the sinuses is less challenging than in the lungs. Based on the above mentioned knowledge, it is important to determine whether *P. aeruginosa* can adapt to anaerobic environments in the sinuses. In this study we determined the pO_2 in the maxillary sinuses in CF patients never infected, intermittently infected and chronically infected with *P. aeruginosa* in their lungs as a first step towards determining under which conditions *P.aeruginosa* adapts in the sinuses.

2. Materials and methods

The patients were recruited at the CF Centre in Copenhagen. The CF-diagnosis was based on characteristic clinical features, abnormal sweat electrolytes and the genotype. CF patients planned for sinus surgery were invited to participate in our study. As a control group, we asked non-CF patients who underwent surgery under general anesthesia because their nasal septum needed correction. Patients suffering of acute or chronic rhinosinusitis were excluded from the control group. All invited CF-patients accepted to be included in the study, while two patients who were invited to join the control group denied.

The CF-patients follows a routine with monthly medical examinations including lung function tests and cultures taken from the lower airways. At least every third month blood samples are taken for measurements including antibodies against *P. aeruginosa* (precipitating antibodies).

No standardized guidelines comprising criteria and motivations for sinus surgery in CF patients exist [22]. At our institution we select patients based on the following criteria in descending order:

1. Patients with declining lung function despite intensive antibiotic-chemotherapy and/or increasing antibodies against Gram-negative bacteria despite negative bacteriology in their sputum samples. Especially patients with unknown focus and increasing antibodies against *P. aeruginosa, Achromobacter xylosoxidans* or *Burkholderia multivorans* are given priority. The majority of patients has been operated due to criteria 1, but may also fulfill criteria 2 or 3 as well.
2. Patients who have undergone lung transplantation within the last year.
3. Patients with severe symptoms of rhinosinusitis according to EPOS guidelines [22].