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Impact of acoustic airflow on intrasinus drug deposition: New insights into the vibrating mode and the optimal acoustic frequency to enhance the delivery of nebulized antibiotic

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ABSTRACT

Aim: We investigated the impact of vibrating acoustic airflow, the high frequency ($f \geq 100$ Hz) and the low frequency ($f \leq 45$ Hz) sound waves, on the enhancement of intrasinus drug deposition.
Methods: ^{81m}Kr-gas ventilation study was performed in a plastinated human cast with and without the addition of vibrating acoustic airflow. Similarly, intrasinus drug deposition in a nasal replica using gentamicin as a marker was studied with and without the superposition of different modes of acoustic airflow.
Results: Ventilation experiments demonstrate that no sinus ventilation was observed without acoustic airflow although sinus ventilation occurred whatever the modes of acoustic airflow applied. Intrasinus drug deposition experiments showed that the high frequency acoustic airflow led to 4-fold increase in gentamicin deposition into the left maxillary sinus and to 2-fold deposition increase into the right maxillary sinus. Besides, the low frequency acoustic airflow demonstrated a significant increase of 4-fold and 2-fold in the right and left maxillary sinuses, respectively.
Conclusion: We demonstrated the benefit of different modes of vibrating acoustic airflow for maxillary sinus ventilation and intrasinus drug deposition. The degree of gentamicin deposition varies as a function of frequency of the vibrating acoustic airflow and the geometry of the ostia.

1. Introduction

Rhinosinusitis is an inflammatory disorder involving the lining of the nasal passages and the paranasal sinuses. Sinuses are poorly ventilated cavities within the bones of the face communicating with the nasal fossa *via* the maxillary ostium (Tarhan et al., 2005; Jones, 2001; Fokkens et al., 2012). Chronic rhinosinusitis (CRS) is one of the most common chronic diseases, affecting about 10–15% of the total population with significant impact on quality of life and health care expenditure, and economic impact in terms of absenteeism and productivity (Durand et al., 2011; Laube et al., 2011). CRS is being defined as the presence of two or more symptoms, such as nasal blockage, obstruction, congestion or nasal discharge (anterior or posterior) (Dykewicz and Hamilos, 2010). Compared with people without rhinosinusitis, those with this disease reported more days spent bedridden and more visits to healthcare providers. These findings highlight the significant impact of this health problem on patient quality of life, as well as costs of care to patients and society (Benninger et al., 2010). One of the primary interests of treatment of this disease is to improve the quality of life of the patients and to reduce the considerable financial burden. CRS patients are currently treated according to guidelines, where finally surgery is performed after various preparative treatments, *i.e.* using nasal pump sprays. There is no standard management of CRS. Significant advances in management have been achieved, including endoscopic surgery, newer antibiotics, better diagnostic criteria, image-guided surgical navigation, and the avoidance of external procedures. These advances have improved the treatment of this

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disease process and, for some patients, may lead to a decrease in the frequency, severity, and duration of symptoms and infections. Medical therapy of CRS is a key strategy, with surgery playing a vital adjunctive role. There are, however, several negative factors that are still present after surgery, including potential offending bacteria, fungi, viruses, and the patients' immunologic responses. These factors and others cause many patients to have frequent, recurrent acute infections compounding their chronic sinusitis. To avoid this, studies have been redirected towards determining better treatments with fewer implications. An efficient topical therapy may allow more effective treatment of upper respiratory diseases, preventing sinus surgery or at least delaying the need for sinus surgery. The most frequently recommended medications for treatment of CRS consist in the systemic administration of antibiotics by oral route. Gentamicin, an aminoglycoside active on Gram-negative bacteria and staphylococci, is considered as one of these frequently recommended antibiotics due to its recognized efficacy on rhinosinusitis associated bacteria (Desrosiers et al., 2011; Kalogjera et al., 2003). The effectiveness of topical delivery of pulmonary antibiotics and corticosteroids through the nebulization process has been previously revealed in many studies (Bhattacharyya et al., 2011; Leclerc et al., 2014a). Topical delivery, particularly nebulization, has the advantage over systemic therapy as it minimizes the risk of systemic side effects while increasing the local dose. Therefore, better targeting of nebulized antibiotics into the common sites of infection, maxillary sinuses, could improve clinical outcomes in patients suffering from CRS and minimize the risk of antibiotic resistance in non-targeted areas. Despite the fact that maxillary sinuses are poorly-ventilated hollow organs, several studies have shown the efficacy of nebulized drug to treat sinus disorder (Leclerc et al., 2014a,b; Durand et al., 2012). Recently, we have studied the gentamicin deposition in the maxillary sinuses using 100 Hz acoustic airflow nebulization. In addition, several works focused on the mechanism involved in sinus ventilation, which is a fundamental requirement of aerosolized drug delivery to the sinus cavities. The sinus ventilation and then the intrasinus drug deposition can be provided by medical devices enabled to generate vibrating airflows. The main objective of these medical devices is to add an acoustic airflow to the airborne droplets in order to generate a sufficient pressure gradient to allow the sinus ventilation (Durand et al., 2011; Möller et al., 2011, 2010). The aim of this study is the investigation of the impact of different modes of acoustic airflow on the maxillary sinus ventilation (using a radioactive gas) and the intrasinus drug deposition (using a gentamicin aerosol).

2. Materials and methods

2.1. Anatomic nasal replica

2.1.1. Human plastinated cast

A technique that allows the preservation of most physical properties of anatomical specimens is known as plastination. The human plastinated cast used provides an easy access to the maxillary sinuses due to lateral-paramedian sections (Durand et al., 2011). Its anatomical and aerodynamic behavior closely resembles *in vivo* patterns. Such models were previously characterized anatomically, geometrically and aerodynamically and were successfully used in several aerosol deposition studies (Durand et al., 2011; Leclerc et al., 2014b; Moeller et al., 2009). In this study, the plastinated nasal cast was used to perform radioactive gas ventilation experiments using ^{81m}Kr-gas.

2.1.2. Nasal replica

A nasal replica was created using a stereolithography technique leading to manufacturing of a transparent, water-resistant, non-porous resin replica of the human plastinated cast (Leclerc et al., 2014b; co-development with the DTF medical company). Anatomical and aerodynamic similarities between the nasal replica of the plastinated nasal cast, particularly the geometry of the ostia and maxillary sinuses, was confirmed after performing endoscopy and CT scans. The differences in the dimensions of the individual maxillary ostia (6 mm long with a 2 mm diameter for the RMS and 2 mm long with a 5 mm diameter for the LMS) possessed by the plastinated human cast were reproduced in the nasal replica thanks to a stereolithography technique (Leclerc et al., 2014b). In this study, the nasal replica was used to perform gentamicin aerosol deposition experiments. Compared to the human plastinated cast and human *in vivo* experiments, nasal replica was approved to be used in aerosol deposition study facilitating the washing technique and reducing the drying time (Le Guellec et al., 2014).

2.2. Nebulizing systems

Two nebulizing conditions were studied. The first one delivers a high frequency vibrating acoustic airflow; we define a high frequency acoustic airflow as an acoustic airflow of 100 Hz and above. The commercial medical device used was the ATOMISOR NL11 jet nebulizer associated with an AOHBOX compressor (DTF Medical, Saint-Etienne, France). A nasal plug (C28, DTF Medical, Saint-Etienne, France) attached to the nebulizer ensured its interface connection with nasal replica's nostrils. Nebulization can be performed with or without the addition of the high frequency acoustic pressure waves by using these two possible modes offered with this commercial medical device.

The second nebulizing condition consists in superimposing a low frequency vibrating acoustic pressure wave to the aerosol production; we define low frequency acoustic airflow as an acoustic airflow of frequency of 45 Hz and above. The commercial device used was the PARI SINUS jet nebulizer associated with a PARI SINUS compressor (Pari GmbH, Starnberg, Germany). Vibrating and non-vibrating airflow nebulizations were performed by connecting and disconnecting the vent tubing from the vibration output of the compressor. For aerosol delivery to the nasal fossa, this nebulizer was coupled to the same nasal plug used in the first nebulizing conditions. Thus, the low frequency device was not used according to producer specifications (*i.e.* one nostril in, the other out). In fact, as the aim of this work was the impact of acoustic airflow on intrasinus drug delivery; we needed a same experimental protocol of aerosol administration to the nasal fossa for both low and high frequency devices to avoid biases due to the impact of the nasal plug. Thus, we must underline that the results of intrasinus drug deposition for the low frequency device cannot be representative of data obtained in vivo according to the producer specifications.

2.3. Scintigraphic study of the sinus ventilation

^{81m}Kr-gas continuously administered *via* nasal plug through the human plastinated cast was performed in order to study the impact of the different modes of acoustic airflow on the radioactive gas penetration into the maxillary sinuses (^{81}Rubidium/^{81m}Krypton generator, COVIDIEN IMAGING FRANCE). Ventilation experiments were performed in front of a single-head planar gamma camera (Millennium MPR Gamma Camera; GE healthcare) equipped with a low-energy, high-resolution collimator.

Each nebulizer was coupled to both nostrils of the model *via* a nasal plug (Fig. 1). The output channel of the ^{81m}Kr-gas generator was directly connected to the compressed air pressure supply tubing of the nebulizer. Two movable plates were used to close the maxillary sinuses hermetically during the ^{81m}Kr-gas ventilation experiments (Durand et al., 2001). Several experiments were