RESEARCH PAPER

Impact of Airborne Particle Size, Acoustic Airflow and Breathing Pattern on Delivery of Nebulized Antibiotic into the Maxillary Sinuses Using a Realistic Human Nasal Replica

Lara Leclerc • Jérémie Pourchez • Gérald Aubert • Sandrine Leguellec • Laurent Vecellio • Michèle Cottier • Marc Durand

ABSTRACT

Purpose Improvement of clinical outcome in patients with sinuses disorders involves targeting delivery of nebulized drug into the maxillary sinuses. We investigated the impact of nebulization conditions (with and without 100 Hz acoustic airflow), particle size (9.9 μm, 2.8 μm, 550 nm and 230 nm) and breathing pattern (nasal vs. no nasal breathing) on enhancement of aerosol delivery into the sinuses using a realistic nasal replica developed by our team.

Methods After segmentation of the airways by means of high-resolution computed tomography scans, a well-characterized nasal replica was created using a rapid prototyping technology. A total of 168 intrasinus aerosol depositions were performed with changes of aerosol particle size and breathing patterns under different nebulization conditions using gentamicin as a marker.

Results The results demonstrate that the fraction of aerosol deposited in the maxillary sinuses is enhanced by use of submicrometric aerosols, e.g. 8.155 ± 1.476 mg/L of gentamicin in the left maxillary sinus for the 2.8 μm particles vs. 2.056 ± 0.0474 for the 550 nm particles. Utilization of 100-Hz acoustic airflow nebulization also produced a 2- to 3-fold increase in drug deposition in the maxillary sinuses (e.g. 8.155 ± 1.476 vs. 3.990 ± 1.690 for the 2.8 μm particles).

Conclusions Our study clearly shows that optimum deposition was achieved using submicrometric particles and 100-Hz acoustic airflow nebulization with no nasal breathing. It is hoped that our new respiratory nasal replica will greatly facilitate the development of more effective delivery systems in the future.

KEY WORDS aerosol therapy · drug deposition · maxillary sinuses · nasal replica

INTRODUCTION

Health problems caused by rhinosinusitis constitute a considerable financial burden on society (1,2). Blockage of sinus drainage through infection of the nasal mucosa or impaired mucociliary clearance produces a favorable environment for sinusitis in which pathogens may

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proliferate. Better targeting of delivery of nebulized antibiotics to the maxillary sinuses could improve clinical outcomes in patients with chronic rhinosinusitis disorders. However, such targeting is complex due to the anatomical features of the maxillary sinuses. These cavities are poorly ventilated and only communicate with the nasal fossa via the maxillary ostium, a narrow duct (about 1–5 mm in diameter; 10–15 mm in length) (3). Drug aerosolization is a common therapeutic approach in the treatment of sinuses disorders such as rhinosinusitis since it is painless and safe and offers a number of advantages over systemic therapy (4,5). Several studies have demonstrated clinical benefits (6), although the question has not been extensively clinically investigated.

In this context, it is clearly of interest to achieve a better understanding of any nebulization features allowing specific targeting of the maxillary sinuses while avoiding pulmonary deposition, since the latter involves a risk of side effects. However, the nebulization conditions required to enhance aerosol deposition in the sinuses are not well established (7). For example, particles larger than 10 μm inhaled nasally are known to be deposited in the nasal cavities (FDA guidance, 2002) but no international consensus or guidelines exist regarding the relationship between aerosol characteristics and precise deposition site within the nasal cavities such as the sinuses.

Human intranasal deposition studies are restricted by the risks associated with exposure and by ethical considerations. As an alternative, anatomical models have been proposed, such as cadaver heads (8,9), nasal cavity replicas (10,11) and nasal casts using recent prototyping techniques [fused deposition modeling (FDM) and stereolithography (e.g. the SLA, Viper or SAINT models)] (12,13). While in vitro studies have shown that nebulized particles may be deposited in the paranasal sinuses, this is always at low concentrations due to ostium morphology as well as aerosol characteristics such as size, pressure and flow rate (14–18). Moreover, in a recent study we demonstrated a significant increase in intrasinus drug deposition using acoustic airflow nebulization (100 Hz) of micrometric airborne particles (9).

The aim of this study is to provide a better understanding of the parameters that enable specific drug targeting of the maxillary sinuses. To that end, we assessed and quantified the deposition of gentamicin (aminoglycoside antibiotic, used as a marker) as a function of variations in three nebulization parameters: airborne particle size within the micron and submicron range (230 nm to 9.9 μm), 100 Hz acoustic airflow, and nasal or non-nasal breathing. The experiments were performed on a realistic nasal replica built using a stereolithography technique.

MATERIALS AND METHODS

Nasal Replica

Plastination allows anatomical specimens to be preserved in a physical state approaching that of live physiological conditions with numerous advantages (19). In particular, in plastinated head specimens, anatomical and aerodynamic behavior closely resembles patterns seen in vivo. Moreover, such models have a specific lateral-paramedian section providing easy access to the maxillary sinuses. Such plastinated human specimens were previously characterized anatomically, geometrically and aerodynamically (20) and then used for aerosol deposition studies (9). However, the main limitations of previous specimens of this type were the complexity of the washing steps involved, especially the long drying time (around 2 days) and the time required to obtain specimens (6 months). To overcome these drawbacks, a nasal replica of the human plastinated specimen was created for this study using a stereolithography technique.

First, a precise CT-scan of the plastinated model was obtained (LightSpeed VCT scanner, GE Healthcare, Milwaukee, Illinois, US). 226 DICOM scan images of the CT-scan, corresponding to the entire nasal cavities, were processed using HYCAD software to delimit the outlines of the cavities of interest, namely the frontal, ethmoidal and maxillary sinuses and the nasal fossae. Special care was taken in delineating the ostia, which constitute a critical ventilation pathway. The 226 segmented images were then converted and imported into the SolidWorks® software, a mechanical 3D computer-aided design program. The model was reconstructed step by step in 3D, as shown in Fig. 1, and the replica was then manufactured in transparent, water-resistant, nonporous resin.

Endoscopy and CT scans were performed on the replica in order to assess the anatomical reproducibility of the known human plastinated model. Precise measurements were compared for the critical anatomical regions of the ostia and maxillary sinuses.

Nebulization Systems and Aerosol Characterization

Micrometric, submicrometric and nanometric aerosols were generated using the following medical jet nebulizers: an Atomisor NL20 (DTF Medical, France) and an Atomisor NL11 (DTF Medical, France), a modified SideStream (Philips Respironics, Ref 12NEB400, England), and a Nanoneb (DTF Medical, France). Aerosol particle sizes were expressed as mass median aerodynamic diameter (MMAD) using an electrical low-pressure impactor (ELPI, Dekati Ltd., Finland), as described in a previous study (9).

Fig. 1 Plastic replica made from the plastinated model. (**a**) Plastinated human specimen – (**b**) DICOM scan image – (**c**) SolidWorks® image – (**d**) 3D reconstruction – (**e**) Resin nasal replica.
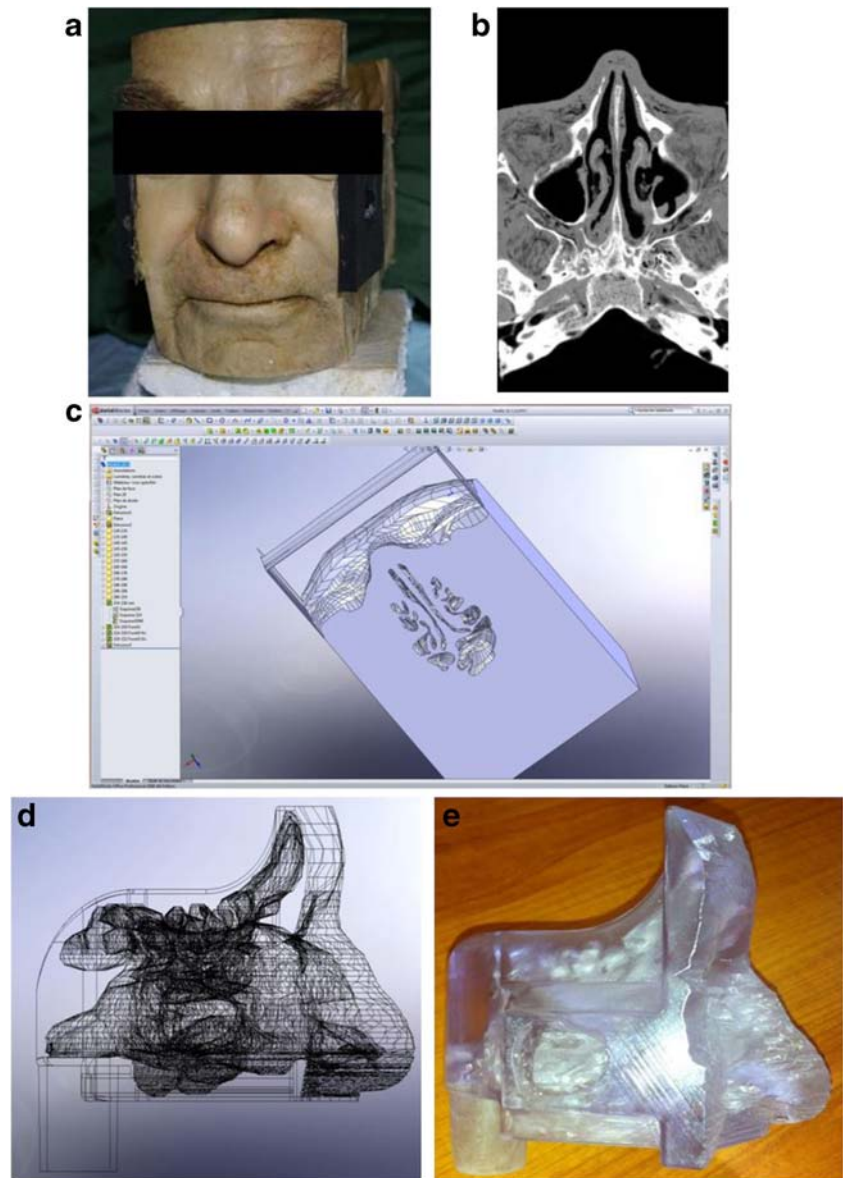
Aerosol characterization was performed using a chemical tracer, sodium fluoride (NaF; 2.5 wt%; 4 mL), as recommended in a European standard (NF EN 13544-1). Operating at an airflow of 10 L.min^{-1}, the ELPI allowed nebulized particles to be sorted into 12 size groups (7 nm to 10 nm). The nebulizer was connected to the ELPI via a metal United States Pharmacopeia (USP) like artificial throat (height 112 mm; width 42 mm; internal diameter 19 mm). NaF was aerosolized by the nebulizer for 10 min, after which the various elements (USP throat and each stage) were rinsed with 5 mL of deionized water. The NaF concentration of samples was assayed by electrochemical means (PerfectION^{TM} combined with a SevenGo pro^{TM} F− electrode, Mettler Toledo, France). Finally, the MMAD and the geometric standard deviation (GSD) of the nebulized particles were calculated using the electrochemical NaF measurements.

Emitted Aerosol Fraction (Output)

The quantity of aerosol produced by the nebulizer over a 10-min period was measured using a residual gravimetric method (21). The mass of gentamicin was measured on a filter before and after nebulization. The results were expressed as the percentage and as the actual mass of gentamicin collected.

Aerosol Inhalation

The experimental set-up is described on Fig. 2 and comprised a nebulizer linked to nasal replica nostrils by a nasal plug (C28, medium size, DTF Medical, France) of a type used in clinical practice. The trachea of the nasal replica was connected to a respiratory pump (Pari, Compas II) allowing reproduction of various sinusoidal breathing patterns. A system of

valves was used with the respiratory pump and the nasal cast to simulate different breathing patterns. A filter was connected to the trachea of the nasal cast to measure the amount of aerosol penetrating into the lung model (Inhalation Filter Pad, Pari GmbH, Germany).

An aminoglycoside antibiotic (gentamicin) was used as the marker (Gentamicin Panpharma, 80 mg/mL, CIP: 3400935120540, Exp: 03/2014, Batch 10267). In each experiment, 4 mL of gentamicin at a concentration of 80 mg/mL was nebulized for 10 min.

The nebulization systems were used with an AOLH® air source compressor (Diffusion Technique Française, DTF Medical, Saint-Etienne, France). This compressor can produce a "sonic aerosol" by adding a 100Hz acoustic airflow during aerosol production as described previously (9). Each experiment was performed both with and without 100Hz acoustic airflow.

Breathing Patterns

Normal nasal breathing

A cycle was defined as 15 breaths per minute, with a tidal volume (Vt) of 500 mL, extrathoracic dead space of 21 ml, tracheal diameter of 1 cm, principal bronchial diameter of 0.8 cm and inspiratory-to-expiratory time ratio (I:E) of 40/60. Under these conditions, inhalation time was set at 1.6 s and exhalation time was set at 2.4 s. These breathing parameters correspond to the reference physiological parameters for male adults (22–24).

Slow nasal breathing

A cycle was defined as a breathing rate of 10 breaths per minute and a Vt of 750 mL. Under these conditions, inhalation time was set at 2.4 s and exhalation time at 3.6 s. Vt values were increased to avoid simulated hypoventilation.

For normal and slow nasal breathing, the set-up simulated inhalation through the nose and expiration through the mouth during operation of the respiratory pump.

No nasal breathing

We compared nebulization without nasal breathing. The same experimental set-up was used but without any cycles. This experimental condition mimics inhalation and exhalation by the mouth.

Drug Deposition in the Maxillary Sinuses

After nebulization, gentamicin was collected from each maxillary sinus by flushing 3 times with the same saline solution using a 1 mL syringe as previously described (9). Gentamicin

concentrations in samples were quantified by fluorescence polymerization immunoassay (FPIA) with a TDxFLx® analyzer (Abbott Diagnostics Division, USA), which has a lower detection limit of 0.2 mg/L. After recovery, the nasal replica was washed copiously with tap water and dried with pulsed air. Control nebulizations were performed with saline solution.

Statistical Analysis

Analysis was performed and graphs plotted using Prism 5.0 software (GraphPad, San Diego, CA). Significance (***) was established by ANOVA test ($p < 0.05$).

RESULTS

Anatomical Features of the Nasal Replica

Nasofibroscopy showed that the nasal replica obtained by stereolithography was similar to the original plastinated human specimen. Endoscopic observations demonstrated good preservation of nasal airway anatomy in the nasal replica. Moreover, physical measurements of the replica confirmed exact reproduction of the plastinated model with a mean error of less than 0.3 mm. For example, between the distance between the right and left sinuses for the plastinated model was 90.88 mm *vs.* 90.51 mm for the nasal replica, and 8.35 mm for the septum in the plastinated nasal septum *vs.* 8.90 mm for the nasal replica. All dimensions were well-respected, especially in such critical anatomical regions as the ostia of the maxillary sinuses.

Imaging data from CT scans confirmed high preservation of anatomy, particularly regarding the nasal airway and turbinate mucosa, which were as close as possible to actual physiological conditions. Figure 3 compares images of the left and right ostia in the plastinated specimen and the nasal replica where the measurements of the structures in the images were identical between the two models. Like the plastinated specimen (9,20), the plastic nasal replica exhibits differences in the dimensions of the individual maxillary ostia: 6 mm long with a diameter of 2 mm for the right maxillary sinus ostium (normal anatomical form: long and narrow) and 2 mm long with a diameter of 5 mm for the left maxillary ostium (abnormally short and broad). These CT and endoscopy results confirm the good preservation of the anatomical and geometrical details in the model, enabling comparison to be made in this study between two different types of ostia morphology.

We earlier determined the reliability of airway geometry (using acoustic rhinometry) and airflow resistance (measured by rhinomanometry) in the plastinated model used as the basis for the stereolithographic nasal replica (20). Taking into account all of these elements, the nasal

Fig. 2 Experimental design for aerosol deposition.
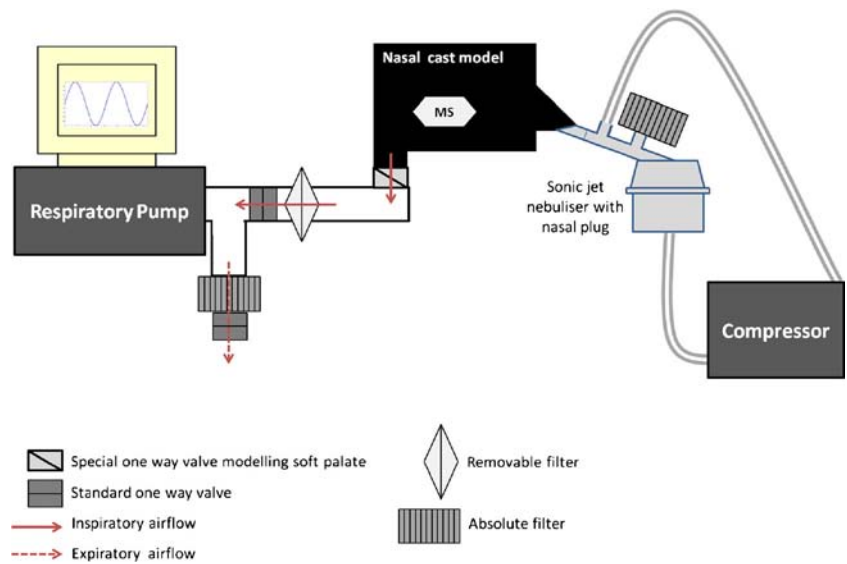
replica manufactured by stereolithography appeared anatomically, geometrically and aerodynamically similar to the original human plastinated specimen, which is a well-validated model of a healthy subject without nasal congestion.

Aerosol Particle Size and Emitted Aerosol Fraction

The results are shown in Table I.

Each type of nebulizer had its own specific aerosol MMAD: 9.9 µm for the Atomisor NL20 (GSD of 2), 2.8 µm for the Atomisor NL11 (GSD of 3.2), 550 nm for the Sidestream (GSD of 2.1) and 230 nm for the Nanoneb (GSD of 1.6).

The emitted aerosol fraction was different for each type of nebulizer: $6.84\pm0.29\%$ for the Atomisor NL20, $9.96\pm1.72\%$ for the Atomisor NL11, $2.06\pm0.46\%$ for the Sidestream and $0.26\pm0.04\%$ for the Nanoneb.

Drug Deposition in the Maxillary Sinuses

All results for gentamicin collected in the maxillary sinuses (mg/L and percentage of the emitted dose) under each test condition (particle size, 100 Hz acoustic effect and breathing

Fig. 3 CT scans performed on the plastinated specimen (**a** and **b**) and on the plastic nasal replica (**c** and **d**). Note preservation of mucosa and different maxillary ostia morphologies (*white arrows*).
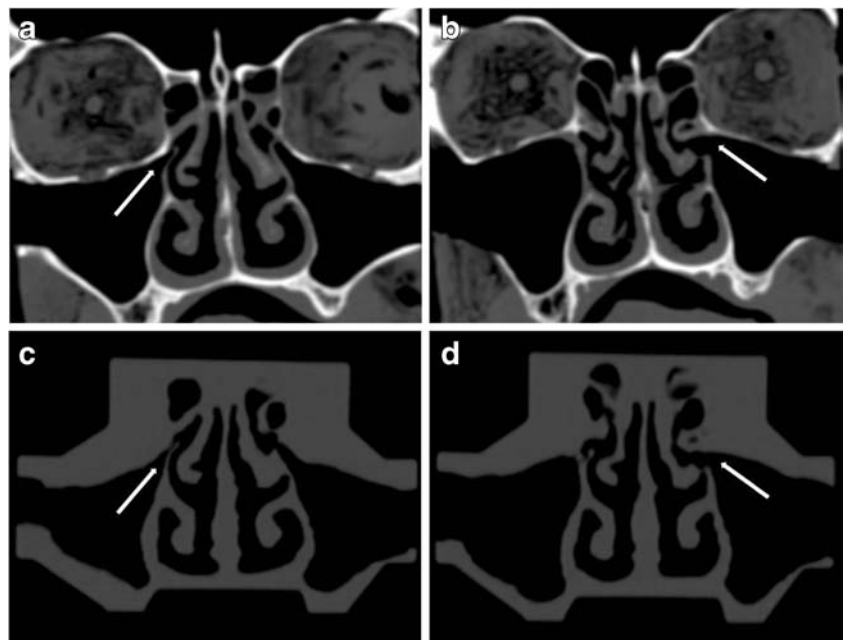
Table I Aerosol Characteristics After 10 min of Nebulization: Mass Median Aerodynamic Diameter (MMAD) Evaluated Using ELPI. Results are Also Expressed as a Percentage of the Emitted Aerosol Fraction and Gentamicin Output Mass (mg)

	MMAD (nm)	GSD	Emitted aerosol fraction (%)	Gentamicin output mass (mg)
NL20	9900	2	6.84 ± 0.29	21.88
NL11	2800	3.2	9.96 ± 1.72	31.89
SideStream	550	2.1	2.06 ± 0.46	6.6
Nanoneb	230	1.6	0.26 ± 0.04	0.83

pattern) are summarized in two tables in the Supplementary Material.

Impact of Anatomy

Aerosols penetrate the maxillary sinuses with different gentamicin deposition profiles due to the anatomical features of the maxillary ostium (Fig. 4a and b). The amount of nebulized active substance collected in the left sinus of the nasal replica was consistently significantly higher for each type of nebulizer in accordance with the morphological differences of the ostia explained in the previous paragraph. These results are perfectly consistent with our previous study (9), and we again confirmed that the airflow resistance associated with the endonasal anatomy has a huge impact on drug deposition in the maxillary sinuses.

Impact of Nebulized Particle Size

The impact of airborne particle size (different MMAD values) is clearly discernible in Fig. 4. Data obtained for the 230 nm size are not exposed on the graphic because values are very close from the detection limit. Since the impact of particle size in aerosols is closely linked to the emitted aerosol fraction, the results shown in Fig. 4a are expressed as percentage of emitted aerosol. We clearly demonstrated that deposition in the maxillary sinuses is enhanced for the smallest particle sizes for a normalized emitted aerosol fraction. Under these conditions, optimal results were obtained with the 230-nm nebulizer, particularly in the left maxillary sinus.

Figure 4b expresses the results in terms of the amount of gentamicin collected in the maxillary sinuses in mg/L. The Nanoneb nebulizer generated particles of around 230 nm and the gentamicin collected in the maxillary sinuses was between 0.2 and 0.4 mg/L, which is very close to the control values (around 0.2 mg/L). The SideStream nebulizer generated particles of around 550 nm and the maximum mean quantity of gentamicin deposited was close to 2 mg/L. Use of larger particles appeared to enhance drug deposition in the maxillary sinuses, with the amount of gentamicin collected for the NL11 nebulizer reaching a mean maximum of 10 mg/L. Finally, the largest particles generated by the NL20 nebulizer (9.9 μm) were deposited to a lesser extent than the 2.8-μm particles (maximum of 2 mg/L in the left maxillary sinus).

Under these conditions, using current nebulization technologies, the particles most efficiently deposited in the maxillary sinuses in terms of mass are those measuring 2.8 μm.

Impact of Breathing Patterns

Figure 5 shows the results for the SideStream and the NL11 nebulizers under normal nasal breathing and non-nasal breathing conditions. No significant differences were noted between normal and slow nasal breathing for the various types of nebulizers (data not shown). By contrast, intrasinus deposition with non-nasal breathing was at least twice as high as with nasal breathing (e.g. in the left sinus: 2 mg/L *vs.* 1 mg/L for the SideStream and 3 mg/L *vs.* 8 mg/L for the NL11).

Impact of 100-Hz Sonic Aerosols

The results concerning the impact of acoustic airflow are shown on Fig. 6. The data shown are for the SideStream and the NL11 nebulizers with and without 100-Hz acoustic airflow. No significant differences were noted for the NL20 and Nanoneb nebulizers (data not shown).

Graphs A and B show that acoustic airflow significantly enhanced gentamicin deposition in both the left and right maxillary sinuses for the SideStream and the NL11 nebulizers with non-nasal breathing. With normal or slow nasal breathing, acoustic airflow had no significant effect for any of the four types of nebulizer.

DISCUSSION

This study assessed the deposition of a nebulized antibiotic in the maxillary sinuses of a nasal replica while varying three following parameters: particle size, 100 Hz acoustic effect and breathing patterns.

The 3D nasal replica manufactured for this study was highly consistent with a plastinated anatomical model that closely resembles a healthy subject without nasal congestion (20). Three main families of human nasal casts exist for the study of aerosol deposition: human cadaver models (16), plastic replicas (12,25) and pipe models (10,26,27). However, these casts have several disadvantages such as biosafety and stability over time for cadaver models and lack of fine detail
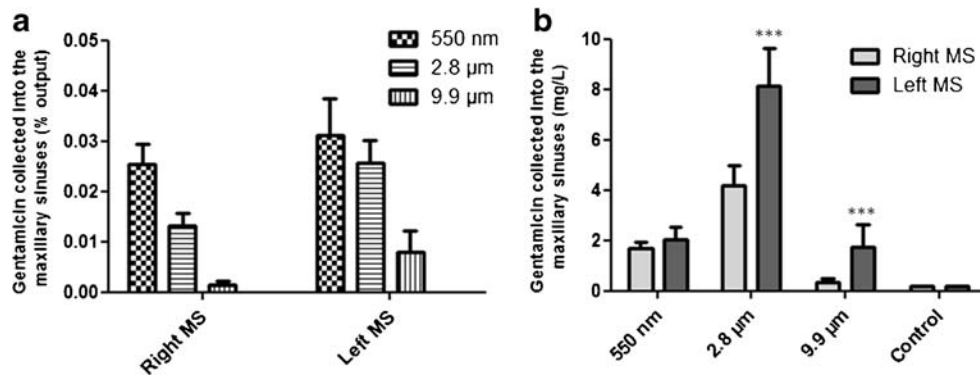
Fig. 4 Impact of nebulized particle size (MMAD) and anatomical features such as right *vs*. left maxillary sinus (MS). (**a**) Amount of nebulized gentamicin collected in the maxillary sinus, expressed as emitted aerosol fraction. (**b**) Amount of nebulized gentamicin collected in the maxillary sinus, in mg/L. Experiments conducted under non-nasal breathing conditions with 100 Hz acoustic airflow. Nebulized physiological saline solution was used as the control ($n = 7$ for each data set, mean $\pm$ SEM, $p < 0.05$).

such as maxillary ostium morphology for plastic replicas and pipe models. The replica of the human plastinated model manufactured for this study appears very useful for *in vitro* characterization of drug deposition in the maxillary sinuses. This model exhibits many desirable technical characteristics such as anatomical features very closely resembling those of *in vivo* human nasal cavities, coupled with ease of access to the maxillary sinuses, stability over several years, ease of washing, ease of handling and transport, absence of odors and biological safety.

We demonstrated that sonic aerosols using a variety of acoustic airflow (w/wo 100 Hz), breathing patterns (nasal *vs*. non-nasal breathing) and particle size (MMAD in the 230 nm-9.9 µm range) lead to disparate intra-sinus drug deposition. These results clearly demonstrate the ability of gentamicin aerosol to penetrate and the maxillary sinuses. We also confirmed the great efficacy of a 100-Hz acoustic airflow in enhancing drug deposition in the maxillary sinuses. These results confirm the conclusions previously described for a single particle size (2.8 µm; NL11) using the human plastinated specimen (9).

Aerosol deposition within the maxillary sinuses appears to be inversely related to aerosol particle size in the 230 nm–

2.8 µm size range (i.e. all except the largest 9.9 µm particles with the NL20 nebulizer). Maximum deposition was achieved with 2.8-µm particles using the NL11 nebulizer. We clearly demonstrated non-significant deposition of the smallest particles generated by the Nanoneb device and weak deposition of the 550-nm and 9.9-µm particles generated by the Side-Stream and NL20 devices respectively. The clear impact of nebulized particle size on the quantity of drug deposited in the maxillary sinuses was observed under non-nasal breathing conditions. In this case, maximum deposition was observed for the 2.8-µm particles (NL11 nebulizer) with an acoustic frequency of 100Hz. It must be noted that for a normalized emitted aerosol fraction, gentamicin deposition of nanometric particles in the maxillary sinuses is enhanced. It suggested the best performance in relation to emitted dose but most of the 230 nm depositions data were very close to the detection limit and therefore should not be over-interpreted. These results are of great interest for the development of new nano-aerosol devices with improved emitted aerosol fractions. For the moment, the NL11 nebulizer seems to be the best compromise for intrasinus targeting.

Interestingly a recent study also presents data of maxillary sinuses deposition in the percentage range of emitted dose
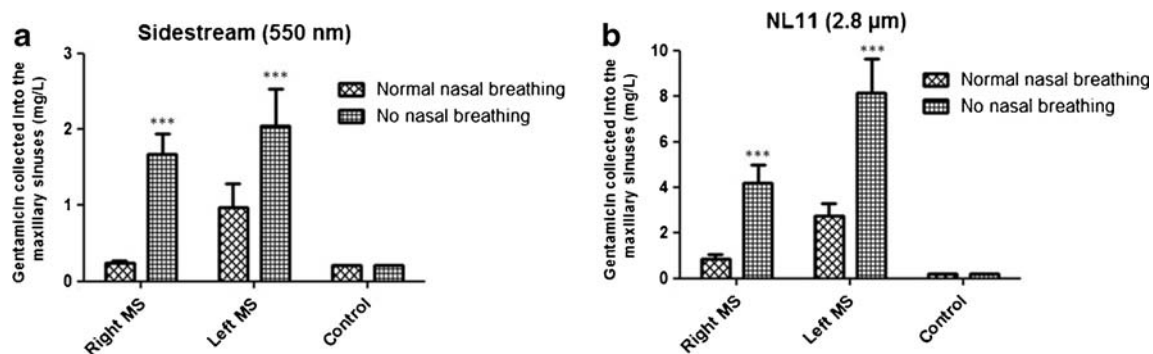

Fig. 5 Impact of breathing patterns on nebulized gentamicin collected in the maxillary sinus (MS) in mg/L. Experiments conducted with 100 Hz acoustic airflow. (**a**) SideStream nebulizer (MMAD: 550 nm). (**b**) NL11 nebulizer (MMAD: 2.8 µm). Nebulized physiological saline solution was used as the control ($n = 7$ for each data set, mean $\pm$ SEM, $p < 0.05$).
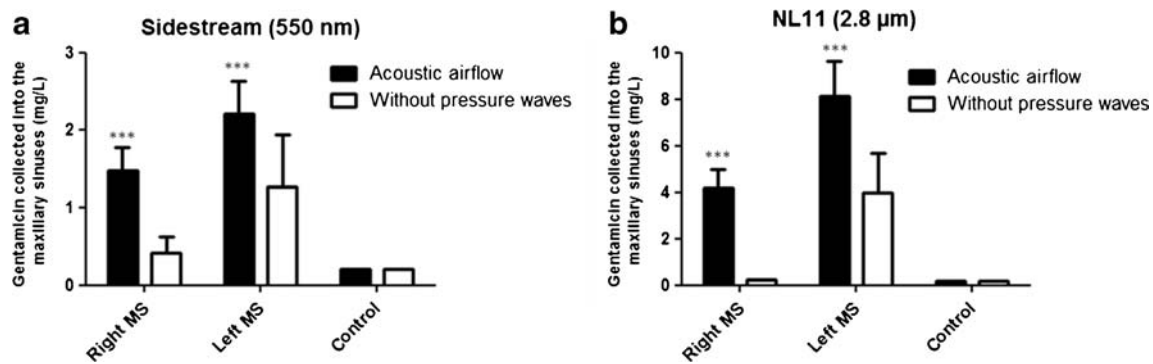
Fig. 6 Impact of 100 Hz acoustic airflow on nebulized gentamicin collected in the maxillary sinus (MS) in mg/L. Experiments conducted under non-nasal breathing conditions. (**a**) SideStream nebulizer (MMAD: 550 nm). (**b**) NL11 nebulizer (MMAD: 2.8 μm). Nebulized physiological saline solution was used as the control ($n = 7$ for each data set, mean $\pm$ SEM, $p < 0.05$).

(28). Sinus deposition data are obtained *in vivo* by means of a radiolabelled aerosol study in patients. Results are approximately 10 times higher than gentamicin deposition obtained in our medication study using a realistic nasal cast. It is however difficult to reach a conclusion because three major parameters change between these studies. 1) Anatomical models are different (*in vivo vs.* realistic nasal cast). The sinus anatomic features appear to be crucial in predicting the maxillary sinuses deposition even if good consistency has been noticed using realistic nasal cast (29,30). Comparison between results of maxillary sinuses deposition obtained using different anatomical model remains difficult. 2) The maxillary sinuses deposition assessment was evaluated by a 2D radiolabelled methodology *vs. in situ* dosage of intrasinusal lavage. 2D radiolabelled quantification is very useful for comparing devices but seems to significantly over-estimate deposition in comparison to other methodologies such as 3D SPECT-CT and intrasinusal lavage (31) and a comparison remains difficult. 3) The nebulization devices are also different and should probably have a strong influence on the deposition (DTF *vs.* PARI Pharma GmbH).

No differences were observed between normal and slow nasal breathing, even with different particle sizes. By contrast, intrasinus drug deposition was significantly enhanced under non-nasal breathing conditions compared to nasal breathing. These results suggest that the increase in aerosol velocity due to nasal breathing leads to significantly decreased intrasinus drug deposition, underlining the potential value of advocating non-nasal breathing to patients for therapeutic ends.

Our approach is based on the fact that in patients with chronic rhinosinusitis, the ostium of the maxillary sinus is obstructed. Thus, the quantity of antibiotic measured within the maxillary sinus is in fact found at the ostium, which constitutes the "crossroads" of sinus disease (since all gentamicin deposited in the maxillary sinus in our model of a non-congested healthy subject clearly entered the maxillary sinus via the ostium). In addition, for subjects undergoing sinus surgery, meatotomy may enable greater quantities of antibiotic to be deposited in the maxillary sinus than those measured

in our model. In either case (operated and unoperated subjects), our results, although obtained in a model of a healthy non-congested subject, are encouraging as regards the potential efficacy of nebulized antibiotics in the treatment of chronic rhinosinusitis, and they demonstrate the relevance of clinical trials on this subject, which should begin in the near future.

While delivery of effective doses of drug continues to be limited by nebulizer technology, micrometric nebulizers such as the NL11 jet appear to offer the best currently available solution for improved drug delivery in sinus patients. In this conditions addition of a 100 Hz acoustic airflow is also recommended.

CONCLUSION

We demonstrated that optimal gentamicin deposition in the maxillary sinuses was obtained with the NL11 nebulizer (MMAD: 2.8 μm) using 100-Hz acoustic airflow and non-nasal breathing. This finding indicates that a specific aerosol pattern should be selected in order to fully enhance intrasinus deposition. Providing patients with specific recommendations concerning the nebulization procedure could thus significantly improve the efficacy of antibiotic treatment.

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