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Sonic aerosol therapy to target maxillary sinuses

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Abstract

Aim: Intranasal aerosol administration of drugs is widely used by ENT specialists. Although clinical evidence is still lacking, intranasal nebulization appears to be a promising therapeutic option for local drug delivery, targeting anatomic sites beyond the nasal valve. The sonic nebulizer NL11SN associates a 100 Hertz (Hz) sound to the aerosolization to improve deposition in the nasal/paranasal sinuses. The aim of the present study was 1) to evaluate in vivo the influence of associating a 100Hz sound on sinus ventilation and nasal and pulmonary aerosol deposition in normal volunteers, and 2) to quantify in vitro aerosol deposition in the maxillary sinuses in a plastinated head model.

Material and methods: Scintigraphic analysis of ^{81m}Kr gas ventilation and of sonic aerosol (^{99m}Tc -DTPA) deposition using the NL11SN was performed in vivo in 7 healthy volunteers. In parallel, NL11SN gentamicin nebulization was performed, with or without associated 100Hz sound, in a plastinated human head model; the gross amount of gentamicin delivered to the paranasal sinuses was determined by fluorescence polarization immunoassay.

Results: Associating the 100Hz sound to ^{81m}Kr gas ensured paranasal sinus ventilation in healthy volunteers. ^{99m}Tc -DTPA particles nebulized with the NL11SN were deposited predominantly in the nasal cavities (2/3, vs. 1/3 in the lungs). In vitro, the use of NL11SN in sonic mode increased gentamicin deposition threefold in the plastinated model sinuses ($p < 0.002$); the resulting antibiotic deposit would be sufficient to induce a local therapeutic effect.

Conclusion: The NL11SN nebulizer ensured preferential nasal cavity aerosol deposition and successfully targeted the maxillary sinuses.

Keywords: sonic aerosol; 100 Hertz; scintigraphy; healthy volunteers; plastinated head model; nasal; sinus; rhinosinusitis.

1. Introduction

Although the efficacy of nebulizing pulmonary antibiotics and corticosteroids has been demonstrated in many studies [1,2], nebulization of antibiotics with a nasal target remains controversial [3,4]. The French health products safety agency AFSSAPS does not recognize an indication for local antibiotics in rhinosinus pathology [5]. In theory, however, nebulization has the advantage over classic administration routes of delivering the drug directly to the target organ, thereby avoiding systemic side-effects while increasing the local dose. Consequently, despite a relative lack of clinical evidence and the small number of published studies, nasal nebulization is in fact frequently used in ENT and by family doctors [6,7]. Nasal aerosol therapy is used in most acute and chronic nasal cavity and sinus pathologies, enabling direct application to the rhinosinusal mucosa, with a rapid clinical response and minimal side-effects. It is particularly used in failure of reference per os or spray treatment [6,8]. Nebulization may indeed be an interesting treatment option in nasal antibiotherapy [9,10].

There are currently no nasal antibiotic sprays; sprays, moreover, fail to target potentially infected anatomic sites such as the maxillary sinus, ethmoid cells or middle turbinate [11,12]. As nebulizers produce finer particles than sprays (4 μ m vs. 30 μ m), they can target anatomic areas beyond the nasal valve, but still fail to reach the maxillary sinuses. Associating a 100Hz acoustic wave, however, enhances ventilation [13] and aerosol deposition [14] in the sinonasal cavities. Nasal sonic nebulizers would thus seem to generate the best adapted aerosols for local treatment of rhinosinusitis.

The present study sought to quantify respiratory pathway and maxillary sinus deposition of the aerosol produced by a nasal sonic nebulizer, NL11SN (DTF, Saint Etienne, France) designed to optimize nasal cavity and maxillary sinus deposition by associating a 100 Hz

sound to the aerosol [15]. Results with the system are reported (i) in vivo in healthy volunteers, using a radioactive tracer, and (ii) in vitro with gentamicin in a plastinated human head model.

2. Material and Methods

2.1. Nasal sonic nebulizer

Nebulization used an ATOMISOR NL11SN (NL11SN) nasal sonic nebulizer with an ATOMISOR AOHBOX® compressor (DTF Médical, Saint-Etienne, France). The aerosol was administered via flexible C28E nasal plugs (DTF Médical, Saint-Etienne, France).

2.2. Healthy volunteer scintigraphy study.

2.2.1. Study population

This single-center study included 7 healthy male, non-smoking volunteers aged 21 to 36 years, with a mean height of 181 ± 3 cm and mean weight 77 ± 10 kg.

The study design was approved by the ethics committee of the Saint Luc University Clinics of the Catholic University of Leuven (UCL, Belgium), where the study was performed. In line with the Declaration of Helsinki and good clinical practice guidelines, the healthy volunteers signed their written informed consent before final inclusion.

The subjects were judged healthy at the first selection consultation after a complete medical check-up comprising physical examination, vital signs assessment, medical and surgical history and inclusion/exclusion criteria: the pulmonary scintigraphy examination required

subjects to be equivalent in sex, age, height and weight so as to limit and harmonize thoracic tissue attenuation within the study population.

The main grounds for exclusion were history of cardiovascular pathology, allergy, asthma or other pulmonary pathology or any ENT, and especially rhinosinusal, pathology (polyposis or any type of rhinosinusitis) or ENT or head and neck surgery (whether repair or functional).

The clinical examination was completed by nasal cavity rhinoscopy; subject 3 showed right nasal deviation and subject 5 a right septal spur, but these were considered to be anatomic variants not entailing exclusion.

2.2.2. Scintigraphic ventilation study of the contribution of a 100 Hz sound

Krypton 81m (^{81m}Kr) ventilation was performed to study the effect on maxillary sinus penetration of associating a 100 Hz sound and to determine the anatomic upper airway and lung regions. ^{81m}Kr gas ($^{81}\text{Rb}/^{81m}\text{Kr}$ generator, Covidien, Petten, Netherlands) was continuously administered via nasal plugs to achieve upper and lower airway ventilation.

The following 2-min scintigraphic acquisitions were performed using a STARPORT 400 AC/T gamma camera (General Electric, Horsholm, Denmark):

- *Gas-1*: nasal cavities on right lateral head view;
- *Gas-2*: nasal cavities on AP head view on ventilation without sound;
- *Gas-3*: nasal cavities on AP head view on ventilation with 100 Hz sound;
- *Gas-4*: lungs on posterior thorax view.

2.2.3. Sonic ^{99m}Tc -DTPA aerosol deposition study

The NL11SN nebulizer was loaded with a 3 ml solution containing 25mg DTPA (Diethylene-Triamine Penta-Acetic Acid) with 74 MBq Technetium 99m (^{99m}Tc) tracer (TechneScan DTPA, Mallinckrodt Medical, Petten, Netherlands).

Ahead of the aerosol session, subjects were trained to inhale the aerosol by the nose and breathe out by the mouth. An absolute filter system (BB50TE, Pall Medical, France) protected the ambient air and quantified exhaled aerosol activity. Nebulization was associated to a 100 Hz sound for 10 minutes.

Immediately after inhalation, the subject sat face to the camera for 3 acquisitions:

- *Aerosol-1*: nasal cavities on right lateral head view;
- *Aerosol-2*: thorax on posterior view;
- *Aerosol-3*: residual nebulizer and accessory activity.

2.2.4 Image processing

Total deposited airway activity was calculated on the activity-balance method, consisting in subtracting non-deposited activity from the activity initially introduced in the nebulizer. Results were corrected for background noise and radioactive decay.

Regions were traced around the anatomic areas of interest (nasal cavities, lungs, stomach) from the ventilation images and applied to each deposition image. Percentage aerosol deposition per region of interest was calculated from the total deposited activity. Deposited DTPA mass (μg) was also determined for each region from the DTPA mass initially introduced in the nebulizer.

2.3. In vitro gentamicin sonic aerosol deposition study

Intranasal concentrations of an antibiotic, gentamicin, nebulized with and without associated 100 Hz sound, were compared in a plastinated head anatomic model.

2.3.1. Plastinated head anatomic model

The human head plastination technique developed and adapted for ENT modeling in the anatomy laboratory of the Saint-Etienne Medical School (France) was used to create several plastinated specimens, three of which were dedicated to functional sinonasal cavity studies [16,17].

The plastinated anatomic specimens were obtained following the usual stages of this technique: specimen preparation (3 days), formaldehyde fixation (3 months), dehydration and degreasing with acetone (1-2 months), silicone impregnation (10-20 days), and polymerization (2-3 months). The polymerization was optimized to avoid tissue retraction [17]. The plastinated heads were validated as aerosol deposition models after anatomic, geometric and aerodynamic analysis, using classical clinical techniques: rhinoscopy, endoscopy, CT, rhinomanometry and acoustic rhinometry.

The models' maxillary sinuses were opened using a sagittal cut involving the lateral sinus wall. Two movable plexiglass plates were used to close the sinuses hermetically during nebulization (Figure 1). This gave access to the sinus antrum to collect the deposited aerosol.

2.3.2. Gentamicin nebulization

Gentamicin (Gentallin[®], Schering-Plough SAS, Courbevoie, France), an aminoglycoside active on Gram-negative bacteria and staphylococci, with recognized efficacy on the bacteria implicated in rhinosinusitis [18,19], was chosen as marker for its solidity and specific deposition on routine methods. Two concentrations were used: 40 and 80 mg/ml.

The NL11SN nebulizer was loaded with 4 ml gentamicin and connected to the model nostrils via nasal plugs (Figure 1).

Nebulization lasted 10 minutes. The plexiglass plates were then withdrawn and the maxillary sinuses were given 4 rinses of 1 ml physiological saline by syringe to collect the gentamicin

deposited on the sinus walls. The rinse liquid was kept at -20°C for subsequent measurement of the collected gentamicin.

After each nebulization, the specimen was liberally washed and dried in free air for at least 48 hours.

Nebulization (n= 112) was performed either in sonic mode (with 100 Hz sound) or classical mode (without sound). Physiological saline nebulization (n=34) was used to check wash-out: i.e., that no gentamicin remained in the sinuses.

2.3.3. Gentamicin assay

Gentamicin was assayed on 291 sinus rinse liquid samples by immuno-enzymatic analysis (fluorescence polarization immunoassay) on a TDX/FLX® device (Abbott Diagnostics, Rungis, France). Assays were performed in triplicate using Gentamicin® reagents (Abbott Laboratories, Diagnostic Division, EU) with sensitivity of 0.27mg/L.

2.4. Statistical analysis

The impact of a 100 Hz sound on gentamicin sinus deposition in the plastinated head model was assessed by t test (XLSTAT®). The significance threshold was set at $p < 0.05$.

3. Results

The in vivo inhalation sessions ($^{81\text{m}}\text{Kr}$ ventilation and $^{99\text{m}}\text{Tc}$ -DTPA nebulization) were well tolerated by all subjects, and there were no adverse events. The upper and lower airways could be visualized with the $^{81\text{m}}\text{K}$ gas in all cases. The recorded images testified to a positive impact on maxillary sinus penetration of associating the 100 Hz sound to ventilation (Figure 2, Gas-2 and Gas-3).

The images also enabled anatomic regions to be defined in the upper airways and lungs, so as to quantify sonic aerosol deposition of nasally inhaled $^{99m}\text{TcDTPA}$ (Figure 1, Aerosol-1).

In terms of $^{99m}\text{Tc-DTPA}$ mass, respiratory pathway aerosol distribution was $2,400 \pm 475 \mu\text{g}$ in the upper airways (nasal cavities and rhinopharynx) and $925 \pm 425 \mu\text{g}$ in the lungs, demonstrating effective targeting of the nasal cavities (two-thirds of the activity) as compared to the lungs. These upper airway calculations took account of swallowing and nasal clearance (Table 1).

The images, however, showed only a small amount of aerosol in the maxillary sinuses, far less than the krypton seen to penetrate them under ventilation scintigraphy. Valid image processing to quantify maxillary region aerosol deposition precisely was not feasible due to the difficulty of situating the regions anatomically.

Little radioactive DTPA ($0 \pm 25 \mu\text{g}$) was found in the stomach, indicating that little aerosol was swallowed during the nebulization session.

In vitro, the 112 gentamicin nebulizations and iterative rinsing did not affect the plastinated head anatomy. Absence of gentamicin in the sinuses was checked by assaying the sinusal liquid collected after physiological saline (result: $< 0.27\text{mg/l}$).

The results detailed in Table 2 show an up to 3-fold increase ($p < 0.05$) in gentamicin concentration in the maxillary sinuses when the 100 Hz sound was associated to nebulization, for both types of concentration tested. Deposition was significantly greater in the left than the right sinus, with or without associated sound ($p < 0.05$).

4. Discussion

The interest of associating a 100 Hz sound to nasal administration was studied first directly in healthy volunteers by in vivo ^{81m}Kr ventilation scintigraphy. The gas was delivered nasally by

an NL11SN nebulizer, and nasal cavity ventilation was recorded laterally before and during the addition of sound. The images (Figure 2, Gas-2 and Gas-3) display the impact of associated 100 Hz sound on maxillary sinus penetration, enhancing ventilation with increased gas exchange between nasal cavities and maxillary sinuses.

A drug aerosol, however, may show different aerodynamic behavior from a gas, with consequently varying impact of 100 Hz acoustic vibrations. The airway distribution of the nasally inhaled sonic aerosol was therefore studied using ^{99m}Tc -DTPA as radioactive tracer. The mass of ^{99m}Tc -DTPA deposited in the upper airways and lungs was calculated for anatomic regions defined on the ventilation images. Two-thirds of the sonic ^{99m}Tc -DTPA aerosol was distributed in the upper airways, and one-third in the lungs. Within the nasal cavities, aerosol deposition stretched from the nasal vestibule to the pharynx (Figure 2, Aerosol-1), rather than being restricted to the first centimeters of the nasal fossae as usually described in the literature [11], which implies that it passed through the middle and inferior nasal meati.

This in vivo study, however, involved limitations, one methodological and the other related to the use of healthy subjects. The methodology provided only overall quantification of upper airway deposition, without detailed differentiation of deposition in therapeutic target sites such as the maxillary sinuses. The proximity of the maxillary sinuses to the nasal fossae makes precise localization within the upper airways as a whole difficult [17,20], especially due to the Compton Effect. This means that the theoretic treatment efficacy of target deposition cannot be assessed. Moreover, the healthy volunteers themselves represented a limitation to the study of the targeting of areas of therapeutic interest, as their maxillary ostia were open (as seen on ^{81m}Kr ventilation) unlike in the general case of patients with rhinologic pathology: patients likely to be concerned by nasal antibiotherapy for chronic rhinosinusitis will generally have a closed ostium [21].

The second, in vitro, study examined the effect of associating a 100 Hz sound to a gentamicin aerosol in a plastinated human head model. Plastination provided a model conserving the mucosa, anatomy and aerodynamics of the nasal cavities and sinuses. Moreover, the active substances nebulized and deposited in the maxillary sinuses could be assayed in situ.

The results demonstrated that the gentamicin nebulized by the NL11SN penetrated and was deposited in the model's maxillary sinuses. The main factor affecting sinusal deposition was the 100 Hz sound, in presence of which the gentamicin concentration collected from the sinuses was significantly increased, by a factor of 1.6 to 3 (Table 2). For a given gentamicin dose, the increase in sinus deposition was equivalent in the 2 sinuses, although the absolute amount of deposit was significantly different between the two ($p < 0.05$), probably due to geometrical differences between the left and right maxillary sinus ostia. Rhinomanometric measurements taken on the same model showed greater right than left ostium resistance [17,22]. The gain in maxillary gentamicin deposition provided by the associated sound was independent of ostium geometry.

Although the model enabled sinus deposits to be collected, it involved certain limitations. The gentamicin assay results were highly variable, due to the technical difficulty of rinsing the sinuses with physiological saline to collect the gentamicin. However well controlled the technique, sinus antrum anatomy and the uneven aerosol deposition over the cavities meant that collection was neither exhaustive nor strictly reproducible from one trial to another.

Moreover, sinus rinsing was suboptimal, as it included neither the lateral wall of the maxillary sinus nor any possible physical gentamicin absorption by the plastinated sinus mucosa; the real quantity of deposited gentamicin in the sinuses was therefore once again inevitably underestimated.

There was further a technical limitation inasmuch as the plastinated head specimen was not ventilated and thus was "passive" under aerosol administration. Inhalation and exhalation of the aerosolized particles was not reproduced, which may have affected the deposition kinetics as compared to a ventilated model. This lack of "respiration" might reduce or on the contrary increase sinus penetration: the former, as airflow through the nasal cavities under inspiration (acceleration) and expiration (vortex) maintains sinus aeration, enabling gas exchange with the nasal cavities (sinus respiration) [21,22,]; or the latter, due to aerosol accumulation in the nasal fossae, increasing penetration into the maxillary sinuses via the ostia.

Nasal antibiotic nebulization is especially controversial due to a lack of data as to the quantity of active molecules actually deposited, their potential clinical efficacy and the expected therapeutic doses.

The present in vivo results in healthy subjects and in vitro results in the plastinated model showed the NL11SN sonic nebulizer to be suitable for targeting the upper airways, including the sinus cavities.

The plastinated head model could be useful for initial assessment of the theoretic efficacy of an antibiotic deposit in the maxillary sinuses according to the quantities of active substance collected. In the present study, a mean 1.35 mg/L and 2.33 mg/L were measured in the rinse liquid from the right and left sinuses respectively, corresponding to a mean mass of 3.31 µg collected from the sinuses.

In terms of deposition efficacy, it is possible to estimate whether the quantity of deposited gentamicin was sufficient to ensure a local therapeutic effect. Sinus gentamicin deposition can be compared to the recognized effective pulmonary deposition of a reference aminoglycoside by normalizing deposition per unit tissue area. Among the aminosides used in nebulization, tobramycin (TOBI®) shows recognized efficacy in *Pseudomonas aeruginosa* pulmonary

infection in mucoviscidosis patients. In vivo studies reported about 45 mg tobramycin deposited in the lungs using the reference pneumatic nebulizer [1].

From these data, the tobramycin deposition rate in the lungs can be estimated at $0.0346 \mu\text{g}/\text{cm}^2$ (for a maximum deposition area of 130 m^2).

If the maxillary sinus is assimilated to a sphere of about 17 cm^3 (mean = 15 to 20 cm^3 in the literature) [23,24,25], the potential aerosol deposition area in a sinus will be 31.93 cm^2 .

Gentamicin deposition in the plastinated head sinuses was estimated at $0.05183 \mu\text{g}/\text{cm}^2$.

According to these new data, the quantity of gentamicin deposition in the in vitro model sinuses can be estimated as being 1.5 fold greater ($0.05183 \mu\text{g}/\text{cm}^2$ vs. $0.0346 \mu\text{g}/\text{cm}^2$) than the reference aminoglycoside deposition in the lungs. Thus, on this initial approach, the quantity of gentamicin collected from the maxillary sinuses would seem to be sufficient to induce a local anti-infection effect. These results should be confirmed in a clinical assessment of the therapeutic efficacy of antibiotic deposition by nasal sonic aerosol.

5. Conclusions

The present study showed that sonic nebulization (i.e., nebulization coupled to a 100 Hz sound), as implemented using the NL11SN nebulizer, optimized aerosol deposition in the nasal cavities (two-thirds of activity) and effectively targeted anatomic regions of interest such as the maxillary sinuses. Maxillary sinus penetration proves passage through the middle meatus, the center of sinus pathology. Thus the nasal sonic aerosols produced by the NL11SN can treat certain rhinosinus pathologies.

By comparison with the results for pulmonary deposition normalized per unit of tissue area, the amount of sinus drug deposition seems sufficient to induce a local anti-infection effect.

The plastinated human head seems to be a useful model for therapeutic assessment of the

theoretic efficacy of sinus deposition of drugs, and of antibiotics in particular. The results show that rhinologic antibiotic nebulization may be useful, avoiding acquisition of resistance. Clinical studies will be required to validate the treatment efficacy of nebulized deposition of antibiotics or other molecules using the NL11SN sonic nebulizer in various rhinosinus pathologies (infectious and/or inflammatory), so as to determine clinical applications.

Conflicts of interest:

Sandrine Le Guellec: Researcher for DTF-Aerodrug, employed by DTF.

Gilles Chantrel: Manager, DTF.

Laurent Vecellio: Scientific director for DTF-Aerodrug, employed by DTF.

The other authors declare no conflict of interest.

References

- [1] Lenney W, Edenborough F, Kho P, Kovarik JM. Lung deposition of inhaled tobramycin with eFlow rapid/LC Plus jet nebuliser in healthy and cystic fibrosis subjects. *Cyst Fibros* 2011;10(1):9-14.
- [2] Donnelly R, Seale JP. Clinical pharmacokinetics of inhaled budesonide. *Clin Pharmacokinet* 2001;40(6):427-40.
- [3] Desrosiers MY, Salas-Prato M. Treatment of chronic rhinosinusitis refractory to other treatments with topical antibiotic therapy delivered by means of a large-particle nebulizer: results of a controlled trial. *Otolaryngol Head Neck Surg*. 2001;125(3):265-9.
- [4] Videler WJ, van Drunen CM, Reitsma JB, Fokkens WJ. Nebulized bacitracin/colimycin: a treatment option in recalcitrant chronic rhinosinusitis with *Staphylococcus aureus*? A double-blind, randomized, placebo-controlled, cross-over pilot study. *Rhinology* 2008;46(2):92-8.
- [5] Antibiothérapie locale en ORL : Argumentaire. 3.3 Efficacité cliniques des antibiotiques locaux à usage nasal ou sinusal. Agence Française de Sécurité Sanitaire des Produits de Santé, July 2004.
http://www.afssaps.fr/var/afssaps_site/storage/original/application/cf17911a89b9a62c4d777e9a38a2abed.pdf.
- [6] Serrano E. L'aérosolthérapie en ORL. *Revue Française d'Allergologie et d'Immunologie Clinique* 2007;47:508-10.
- [7] De Monte M, Scruignec J, Dubus JC, et al. N.U.A.G.E.S: a survey of nebulisation practice in France with regard to ERS guidelines. *Respir Med* 2007;101(12):2561-5.
- [8] Fokkens WJ, Lund VJ, Mullol J. European Position Paper on Rhinosinusitis and Nasal Polyps. *Rhinology* 2007;45(suppl 20):1-139.
- [9] Vaughan WC, Carvalho G. Use of nebulized antibiotics for acute infections in chronic sinusitis. *Otolaryngol Head Neck Surg* 2002;126:558-68.
- [10] Scheinberg PA, Otsuji A. Nebulized antibiotics for the treatment of acute exacerbations of chronic rhinosinusitis. *Ear Nose Throat J* 2002;81(9):648-52.
- [11] Suman JD, Laube BL, Dalby R. Comparison of nasal deposition and clearance of aerosol generated by nebulizer and an aqueous spray pump. *Pharm Res* 1999;16:1648-52.
- [12] Laube B. Devices for aerosol delivery to treat sinusitis. *J.Aerosol. Med* 2007;20 (1):5-18.
- [13] Maniscalco M, Sofia M, Weitzberg E, Lundberg JO. Sounding airflow enhances aerosol delivery into the paranasal sinuses. *Eur J Clin Invest* 2006;36:509-13.
- [14] Möller W, Schuschnig U, Meyer G, Mentzel H, Keller M. Ventilation and drug delivery to the paranasal sinuses: studies in a nasal cast using pulsating airflow. *Rhinology* 2008;46:213-20.

- [15] Guillerm R, Badre R, Flottes L, Riu R, Fey A. A new method for aerosol penetration into the sinuses. *Presse Med* 1959;30:1097-8.
- [16] Durand M, Rusch P, Granjon D et al. Preliminary study of the deposition of aerosol in the maxillary sinuses using a plastinated model. *J Aerosol Med* 2001;14:83-93.
- [17] Durand M, Pourchez J, Louis B et al. Plastinated nasal model: a new concept of anatomically realistic cast. *Rhinology* 2011;49(1):30-6.
- [18] Kalogjera L, Vagić D, Baudoin T. Effect of endosinus treatment on cellular markers in mild and moderate asthmatics. *Acta Otolaryngol* 2003;123(2):310-13.
- [19] Bhattacharyya N, Kepnes LJ Assessment of trends in antimicrobial resistance in chronic rhinosinusitis. *Ann Otol Rhinol Laryngol* 2008;117(6):448-52.
- [20] Aggarwal R, Cardozo A, Homer JJ. The assessment of topical nasal drug distribution. *Clin Otolaryngol Allied Sci* 2004;29:201-5.
- [21] Eloy P, Nolevaux MC, Bertrand B. Physiologie des sinus paranasaux, EMC-Oto-Rhino-Laryngologie 2005;2:185-97.
- [22] Croce C, Fodil R, Durand M et al. In vitro experiments and numerical simulations of airflow in realistic nasal airway geometry. *Ann Biomed Eng* 2006;34:997-07.
- [23] Emirzeoglu M, Sahin B, Bilgic S, Celebi M, Uzun A. Volumetric evaluation of the paranasal sinuses in normal subjects using computer tomography images: a stereological study. *Auris Nasus Larynx* 2007;34(2):191-5.
- [24] Dah-Jouonzo H, Baron P, Faure J, Treil J, Borianne P. Volumetric measurements of maxillary basal bones and facial air cavities using 3D imagery. *Internationnal Orthodontics* 2005;3 :269-289.
- [25] Paganelli A, Michel J, Varoquaux A, Adalian P, Thomassin J, Dessi P. Etude des variations de volumes des sinus maxillaires en fonction de l'âge et du sexe des individus : applications fondamentales et cliniques potentielles. 117th SFORL Congress, October 2010, Paris, page A106, reference P030.

Figures



Figure 1: Nebulization of gentamicin in a plastinated head model, using the ATOMISOR NL11SN nasal sonic nebulizer connected to an ATOMISOR AOHBOX® compressor.

The pressure input tube ensured continuous compressed air inflow and the sound input tube ensured conduction of the 100 Hz sound produced by the compressor. The sonic nebulizer was connected to the plastinated head nostrils via nasal plugs. The two movable plexiglass plates on either side of the model hermetically closed external access to the maxillary sinuses.

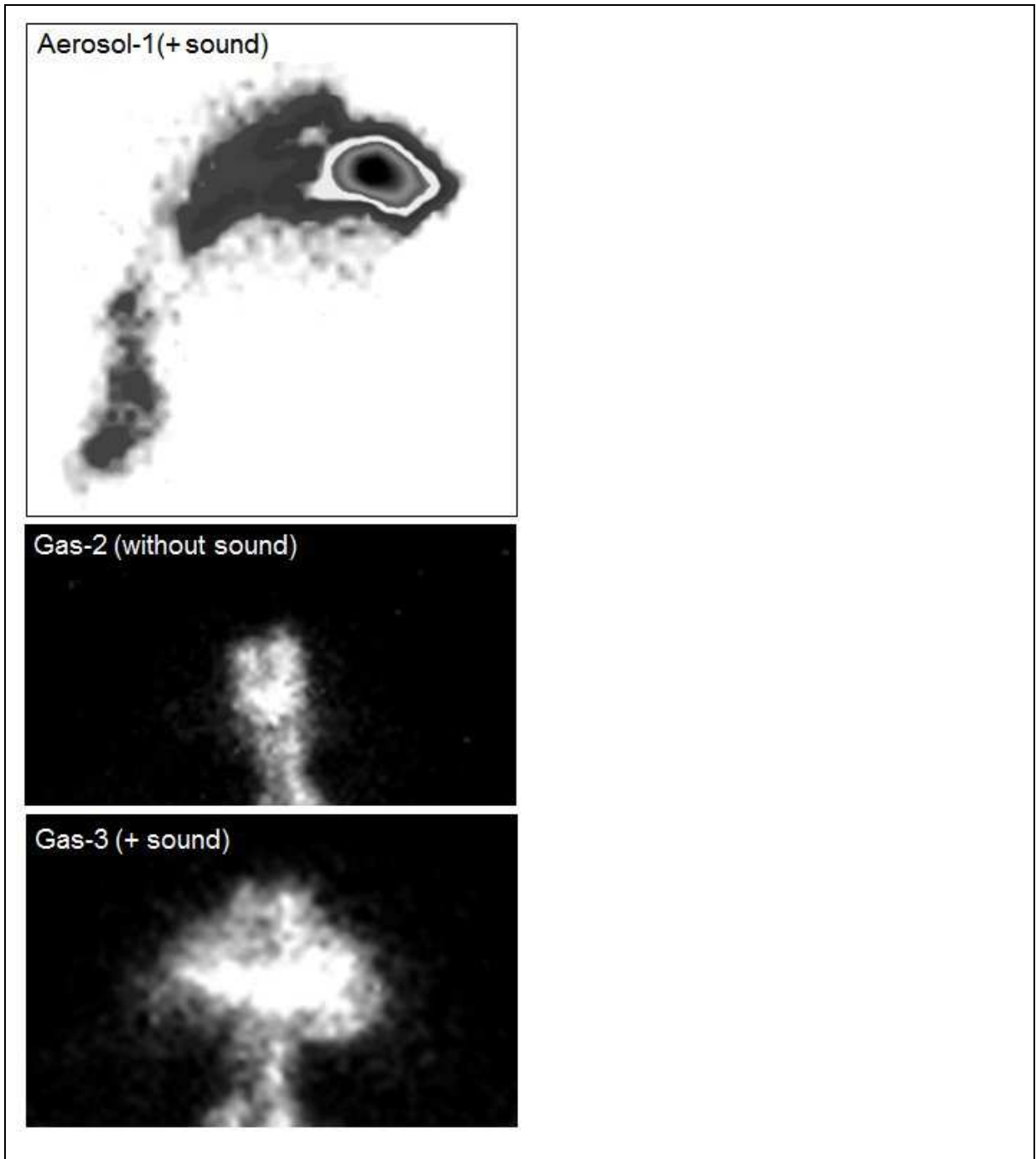


Figure 2: Scintigraphy images in healthy volunteers, using the NL11SN sonic nebulizer and ATOMISOR AOHBOX® compressor:

Aerosol-1: ^{99m}Tc -DTPA aerosol deposition with associated 100 Hz sound (right lateral nasal cavity view);

Gas-2: ^{81m}Kr ventilation without associated sound (anterior side of the nasal cavities);

Gas-3: ^{81m}Kr ventilation with associated 100 Hz sound (anterior side of the nasal cavities).

Table 1: ^{99m}Tc -DTPA aerosol deposit (μg) from NL11SN nebulizer/AOHBOX® compressor, in 7 healthy subjects (mean \pm SD).

Upper airways ^a	2,400 \pm 475
Lungs	925 \pm 425
Stomach	0 \pm 25

^a Upper airways taking account of nasal cavities, rhinopharynx and stomach.

Table 2: Mean gentamicin concentration (mg/l) collected from the left and right maxillary sinuses of the plastinated head model after classic nebulization (without associated sound) and sonic nebulization (with associated 100 Hz sound) for 2 antibiotic formulae (40mg/ml and 80mg/ml), using the NL1 ISN nebulizer/AOHBOX® compressor.

Loaded gentamicin concentration (mg/ml)	Type of nebulization	Gentamicin concentration collected in maxillary sinuses (mg/l)		
		Right sinus	Left sinus	
40	classic	< 0.27 ^a	< 0.27	p = 0.679 **
40	sonic	0.64 ± 0.22	0.73 ± 0.32	p = 0.242 **
		p = 0.002 *	p = 0.005 *	
80	classic	0.63 ± 0.52	1.19 ± 1.03	p = 0.005 **
80	sonic	1.35 ± 0.91	2.33 ± 1.49	p = 0.019 **
		p < 0.0001 *	p < 0.0001 *	

^a mean concentration below assay kit sensitivity threshold (0.27mg/L)

* t test, classic vs. sonic nebulization

** t test, right vs. left sinus