

Evaluation of domestic and Yucatan swine nasal sinus anatomy as models for future sinonasal research of medications delivered by standard instruments used in functional endoscopic sinus surgery

Jay Ching Chieh Wang, BHSc (Honours), Iain Hathorn, MBChB, FRCS (ORL-HNS), Al-Rahim Habib, BSc, Estelle Chang, MDCM and Amin R. Javer, MD, FRCSC

Background: There is a need to find an animal model to study new medications to improve mucosal wound healing after functional endoscopic sinus surgery (FESS). Current literature suggests swine as a potential candidate. The lack of information correlating swine computer tomography (CT) and endoscopic sinonasal anatomy prompted us to investigate them in the domestic and Yucatan swine to determine their feasibility as models to test new medications and drug-embedded stents applied using FESS techniques.

Methods: Two domestic pig heads and 2 Yucatan pig heads were imaged using helical thin slice (1 mm) CT. Two rhinologists analyzed the images and performed endoscopy on the swine. Particular attention was given to accessing the frontal sinus and suturing stents to the nasal septum using standard endoscopic instruments.

Results: CT confirmed that swine sinonasal anatomy is largely similar to human, with all major sinuses present. The middle and inferior turbinates of swine arise from a single uniturbinate. The superior turbinates contain large concha bullosa. Unlike human, swine nasal septum is bone anteriorly and cartilage posteriorly. The frontal sinus ostia, re-

gardless of head size, were consistently around 10 cm from the nasal aperture. On endoscopy, domestic swine frontal sinus ostia were easily accessible for topical medication deposition. Silastic splints can be sutured to the domestic swine septum through the posterior cartilaginous portion, allowing for studies involving medication-eluting material. The narrower nasal cavity of Yucatan pigs prohibited endoscopic maneuvers.

Conclusion: Domestic swine, but not Yucatan, are a feasible model for future sinonasal research using standard FESS instruments. © 2013 ARS-AAOA, LLC.

Key Words:

frontal sinus; swine; X-ray computed tomography; endoscopy; animal models

How to Cite this Article:

Wang JCC, Hathorn I, Habib A-R, Chang E, Javer AR. Evaluation of domestic and Yucatan swine nasal sinus anatomy as models for future sinonasal research of medications delivered by standard instruments used in functional endoscopic sinus surgery. *Int Forum Allergy Rhinol*, 2013; 3:150-156.

An animal model is “a living organism with an inherited, naturally acquired, or induced pathological process that in one way or another resembles the same phenomenon in man.”¹ In the area of pharmaceutical and toxicology research, animal models can be used to determine effect, efficacy, effective dose, toxicity profile, and patho-

physiological interactions of novel medications.¹ In particular, animal models provide a platform through which safety profiles of the new medications can be obtained before testing them in humans.

Research on medications used to improve mucosal wound healing following functional endoscopic sinus surgery (FESS) may also require the use of animal models. Our group is interested in studying the effect of fucoidan on post-FESS synechia, which has been shown in an animal model to reduce the formation of postsurgical adhesion in the abdomen.² This would be particularly useful in the frontal sinus because frontal ostia have a tendency to scar and stenose postsurgery. However, before testing fucoidan in human sinuses, we must first establish the safety profile, absorption, and effect on sinonasal mucosa in an animal model.

Department of Otolaryngology, Sinus Center, St. Paul's Hospital, Vancouver, BC, Canada

Correspondence to: Amin R. Javer, FRCSC, St. Paul's Hospital, Department of Otolaryngology, Sinus Center, Providence 2, 1081 Burrard St., Vancouver, BC, Canada V6Z 1Y6; e-mail: sinussurgeon@drjaver.com

Funding sources for the study: St. Paul's Sinus Center Research Fund. Potential conflict of interest: None provided.

Received: 17 February 2012; Revised: 5 June 2012; Accepted: 26 June 2012
DOI: 10.1002/alr.21081

View this article online at wileyonlinelibrary.com.

We plan to study the effect of fucoidan delivered by 2 methods via standard FESS instruments: drug-incorporated gel, which would be deposited in the frontal sinus of the animal; and drug-embedded silastic stent, which would be sutured onto the nasal septum of the animal models. Thus, it is crucial to choose an animal model that allowed investigators to access the frontal sinus and suture stents onto the nasal septum using the standard FESS instruments.

Many different animal models have been used in FESS-related research, including rabbits,³⁻⁹ sheep,¹⁰⁻¹⁶ and swine.^{17,18} Among these 3 animals, the swine appeared to be the most promising for the following reasons. First, even though rabbits are readily available and easy to breed, their sinuses were too small to accommodate the smallest endoscope we have access to, the 0-degree pediatric endoscope (result from our preliminary trial), for endoscopic maneuvers. On the other hand, sheep and pigs do not have the same problem. However, pigs exhibit a number of advantages over sheep. Sheep nasal cavities have been shown to be too deep for the reach of the standard FESS instruments used in human surgeries.¹⁹ Also, the paranasal sinus anatomy of the sheep differs greatly from human paranasal sinuses.²⁰ While these reasons make sheep a less suitable candidate for our purpose, the work that has been done on swine thus far make pigs a much more attractive choice. Recently, the Witmer Lab of Ohio University constructed a virtual pig head from computed tomography (CT) imaging to establish the detailed sinus anatomy of the swine. Furthermore, previous studies have shown similarities in physiological processes between swine and human, including the molecular responses of mucosal wound healing²¹ and drug absorption of the nasal mucus membrane.²² As such, pigs offer greater potential over sheep and rabbit for use as an animal model in FESS-delivered medication studies.

In this study, we aimed to determine and correlate the CT and endoscopic anatomy of the domestic and Yucatan swine—a comparison which has not been reported before—in order to determine the suitability of using the swine as an animal model to study sinonasal medications in the future. In particular, we are interested in determining the accessibility of the frontal sinus and swine nasal septum for topical drug deposition and suturing of drug-embedded silastic stents, respectively, using standard FESS instruments. These are of specific interest to us due to the higher rate of frontal sinus stenosis post-sinus surgery and because the septum offers a large area of nasal mucosa to assess drug absorption and effect.

Subjects and methods

Criteria for anatomic feasibility

We wished to study the effect of medications both in the form of gel and drug-eluting stents applied to the nose and sinuses. A feasible animal model must therefore satisfy the following 2 criteria:

1. Easy access to the sinuses under endoscopic guidance using standard FESS instruments for deposition of drug-containing gel, and;
2. Ability to suture medically-coated silastic stents on the swine nasal septum.

Swine

Our group chose to study the standard domestic swine as a potential candidate for use as an animal model because they are readily available and affordable.²³ In addition, we also studied the Yucatan miniature swine, as they retain their miniature status over time and may be more suitable for studies involving longer time frames.²⁴

Two domestic swine heads and 2 Yucatan miniature swine heads were obtained from Jack Bell Research Center and International Collaboration on Repair Discoveries (ICORD) Blusson Spinal Cord Center in Vancouver, British Columbia, Canada. The domestic swine were female, and 6 months old. The Yucatan miniature swine were both females, and aged 12 months.

Anatomic evaluation through CT and endoscopy

CT imaging ordered in axial, coronal, and sagittal planes is a routine requisition for patients undergoing endoscopic sinus surgery at St. Paul's Sinus Center (SPSC). The swine heads were imaged under the SPSC protocol, using a GE Low-Dose Lightspeed volume CT (VCT, General Electric, Fairfield, Connecticut) 64-slice system. Scans were analyzed by 2 rhinologists (AJR & IH) for interexaminer comparison to identify any similarities and/or differences between swine and human anatomy. The authors used a methodical approach to assess the domestic and Yucatan swine scans by first evaluating each sinus in succession. Scans in the axial plane were examined by scrolling from superior to inferior to evaluate their anatomical relation to the nasal aperture. Images in the coronal and sagittal planes were evaluated from anterior to posterior and lateral to medial respectively, to determine the orientation of sinus outflow tracts. The inferior, middle, and superior turbinates were identified and followed to their respective points of attachment, making note of pneumatization and overall size. The septum was examined utilizing images in the axial and coronal planes to determine its composition. Measurements were taken in centimeters from the structures of interest, including the frontal sinus and the concha bullosa of the superior turbinate, to nasal aperture, using an electronic ruler.²⁵ As a point to be emphasized, the analyzers also paid close attention to the distance of the frontal sinus from the nasal aperture, as it will be an important site of drug deposition when using the swine as an animal model.

Rigid sinonasal endoscopy was performed utilizing endoscopes of various sizes (3.0-mm 0-degree Karl Storz 7220 AA, 2.8-mm 0-degree Karl Storz, Endoscopy, Tuttlingen, Germany, 7219 BA, and 2.8-mm 30-degree Karl Storz 7219 BA) on the swine heads. A standardized approach, as practiced by the senior author, was utilized to directly

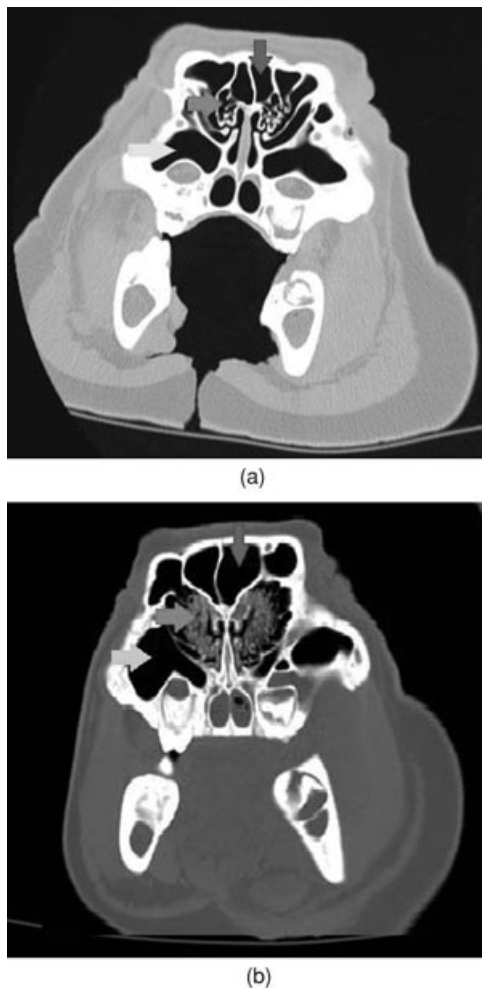


FIGURE 1. (A) Coronal CT section of the domestic swine head at 13.6 cm from the nasal aperture, showing maxillary (yellow arrow), frontal (red arrow), and ethmoid (green arrow) sinuses. (B) Coronal CT section of the Yucatan swine head at 10.6 cm from the nasal aperture, showing maxillary (yellow arrow), frontal (red arrow) and ethmoid (green arrow) sinuses.

visualize the endoscopic anatomy of the swine. This was then correlated to the detailed anatomy as shown on the CT scan. In addition, access to the swine frontal sinus and suturing of silastic stents was performed using regular endoscopic surgical instruments, including 0-degree and 45-degree through-cutting punches.

Results

CT

The CT scans revealed that all of the domestic and Yucatan swine had maxillary, frontal, ethmoid, and sphenoid sinuses present on both sides (Fig. 1A, B). The frontal sinuses in all swine were found to be in a more horizontal plane with the nasal aperture than is the case in humans. This was noted to provide easier endoscopic access than the frontal sinus in humans, which is much more superior in relation to the nose. Both domestic and Yucatan swine nasal septum exhibit anterior septal bone and posterior septal cartilage, which are opposite to the situation in humans.

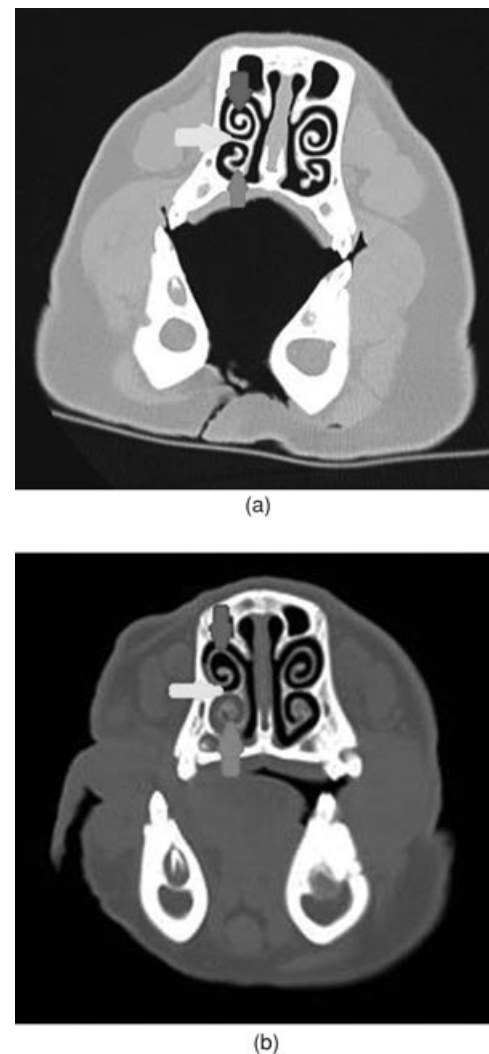


FIGURE 2. (A) Coronal CT section of the domestic swine head at 10.0 cm from the nasal aperture, showing the middle (red arrow) and inferior turbinate (green arrow) arising from a single uniturbinate (yellow arrow). (B) Coronal CT section of the Yucatan swine head at 6.6 cm from the nasal aperture, showing the middle (red arrow) and inferior turbinate (green arrow) arising from a single uniturbinate (yellow arrow).

Also, in contrast to humans, the swine middle and inferior turbinates arise from a single uniturbinate (Fig. 2A, B). In addition, the superior turbinate in the swine exhibits large concha bullosa (Fig. 3A, B). The opening of the frontal sinus appeared to be just adjacent to the superior turbinate and as can be seen on the sagittal CT the frontal sinus is located just above the superior turbinate (Fig. 3C). The frontal sinuses of all 4 swine heads, despite variation in head size and breed, were noted to all be located around 10 cm from the nasal aperture.

The dimensions of the frontal sinuses and cartilaginous septum were noted, and the average values are reported in Table 1.

Endoscopy

The frontal sinuses of both domestic swine heads were visualized using a 0-degree pediatric endoscope (3.0-mm

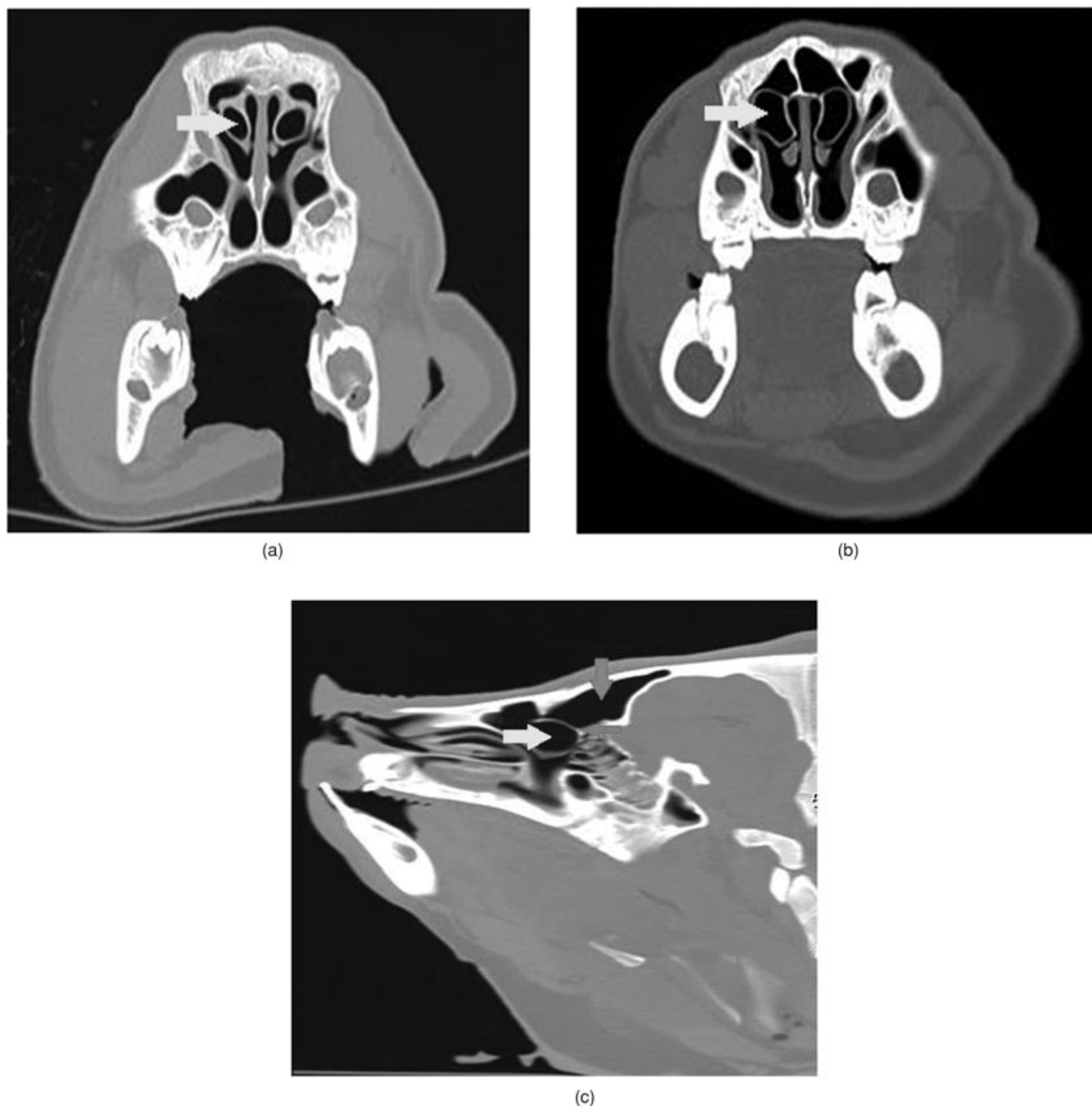


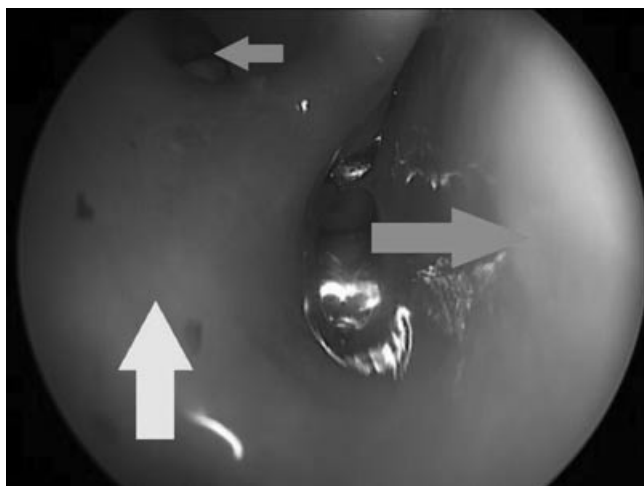
FIGURE 3. (A) This coronal CT section is captured at 10.6 cm from the nasal aperture of the domestic swine. Notice the large concha bullosa (yellow arrow) in the superior turbinate of the domestic swine, which needs to be dissected in order to access the frontal sinus. (B) This coronal CT section is captured at 8.8 cm from the nasal aperture of the domestic swine. Notice the large concha bullosa (yellow arrow) in the superior turbinate of the domestic swine, which needs to be dissected in order to access the frontal sinus. (C) This sagittal CT section of the Yucatan swine head shows the frontal sinus (green arrow) and the concha bullosa (yellow arrow) of the superior turbinate (blue arrow). This section shows that wide access of the frontal sinus could be obtained by opening the concha bullosa.

0-degree Karl Storz 7220 AA, 2.8-mm 0-degree Karl Storz 7219 BA) and standard straight and 45-degree sinus instruments. As was demonstrated on the CT scans, the anatomy of the frontal sinus and its relationship to the nasal aperture made nasal endoscopy much easier than is usually the case in humans. The concha bullosa of the superior turbinate can be visualized using the endoscope (Fig. 4), and its distance from the nasal aperture of 10.6 cm, which was found

on the CT scan, was confirmed by measuring the length of endoscope needed to reach it. The frontal sinus ostium was identified in both domestic swine just adjacent to the superior turbinate concha bullosa (Fig. 4), and is rather small in size. Opening the concha bullosa of the superior turbinate allowed wider access to the frontal sinus (Fig. 5). The frontal sinus can then be accessed through the opened concha bullosa (Fig. 6). A Silastic stent was successfully

TABLE 1. Summary of the parameters of the frontal sinuses and cartilaginous septum obtained from the domestic and Yucatan swine

Swine	Frontal sinus		Cartilaginous septum	
	Height (mm)	Width (mm)	Height (mm)	Length (mm)
Domestic				
Left	18.75	12.8	23.45	87.6
Right	17.95	11.25		
Yucatan				
Left	21	16.4	22.3	77.6
Right	17.4	12.4		

**FIGURE 4.** Endoscopic view of the undissected concha bullosa (yellow arrow) in the right nasal cavity at 10 cm from the nasal aperture. The concha bullosa is an important structure because opening the concha bullosa allows for wide access to the frontal sinus. The nasal septum is indicated with an orange arrow, while the ostium of the frontal sinus is indicated by the green arrow.

sutured onto the nasal septum of domestic swine on the posterior cartilaginous portion, using a 2.0 polydioxanone (PDS) suture on a cutting needle (Fig. 7). When attempting endoscopy on the Yucatan miniature swine, the size of their nasal cavity proved too narrow to allow for endoscopic maneuvers. The 0-degree pediatric endoscopes (3.0-mm 0-degree Karl Storz 7220 AA, 2.8mm 0-degree Karl Storz 7219 BA) became trapped in the nasal cavity approximately 5 cm from the nasal aperture, which was well short of the frontal sinus. Similarly, no space was available to allow instruments to pass for suturing silastic stents (Fig. 8).

Discussion

Swine sinonasal anatomy and access to frontal sinus and nasal septum

The CT scans revealed that the sinonasal anatomy of the swine exhibits various similarities and differences when compared to human sinus anatomy. Similar to humans,

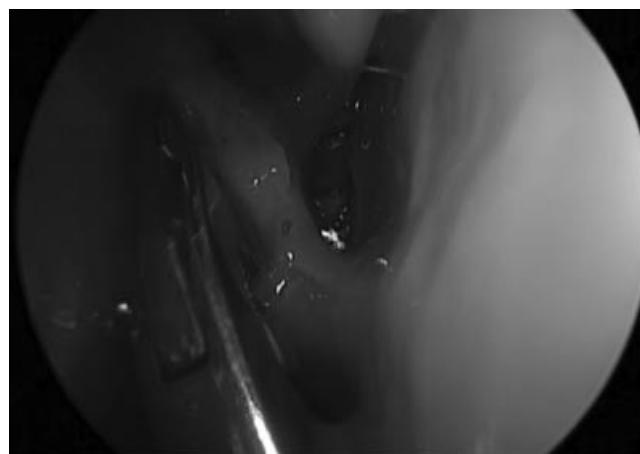
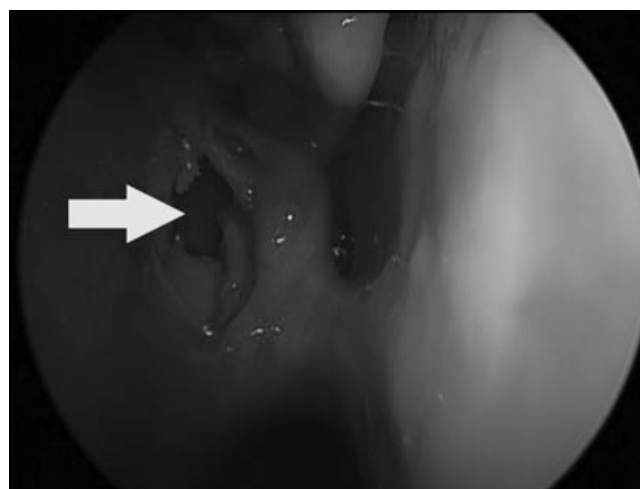
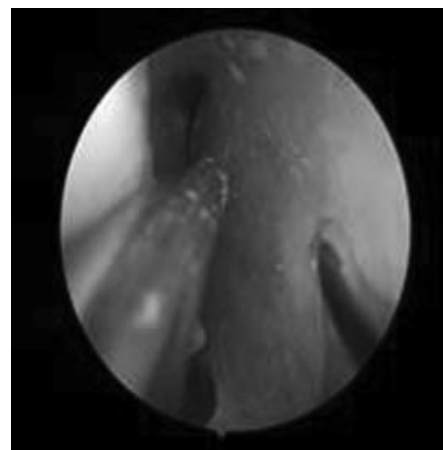
**FIGURE 5.** Opening the concha bullosa to access the frontal sinus using standard endoscopic surgical instruments. This photo was taken in the right nasal cavity of the domestic swine at 10 cm from the nasal aperture.**FIGURE 6.** Endoscopic view of the opened concha bullosa (yellow arrow) in the right nasal cavity at 10 cm from the nasal aperture. The frontal sinus can be accessed through the opened concha bullosa.**FIGURE 7.** A silastic stent securely sutured onto the cartilaginous part of the swine nasal septum.



FIGURE 8. Endoscopic view of inferior and middle turbinate in the left nasal cavity of the Yucatan pig, 4 cm from the nasal aperture. The narrow airway, which prevented further advancement of the endoscope, could not accommodate the simultaneous insertion of an endoscope and a standard FESS instrument.

swine possess maxillary, frontal, ethmoid, and sphenoid sinuses. However, unlike humans, the middle and inferior turbinates of the swine arise from a single uniturbinate, while the superior turbinate demonstrated large concha bullosa. It is important to understand these anatomical features of the swine nasal cavity in order to access the frontal sinus of the swine for drug deposition. In fact, due to the alignment of the frontal sinus in relation to the nasal aperture, the frontal sinus is relatively easy to access compared to that of human frontal sinuses. Furthermore, the swine septum is composed of bone anteriorly and cartilage posteriorly. This is opposite to the situation in humans, in which the anterior septum is cartilaginous and the posterior part is bone (posterior plate of ethmoid and vomer). This finding is significant since the effect of drugs embedded in silastic stents on the wound healing of sinonasal mucous membrane can be studied by suturing the stent on to the nasal septum and followed over time. The cartilaginous septum of the domestic and Yucatan swine examined offered a 23.45-mm × 87.6-mm and 22.3-mm × 77.6-mm surface area, respectively. This provides a large area of nasal mucosa to place stents to study medication safety, absorption, and effect. When planning studies that involves suturing medicated stents on to the swine cartilaginous septum, investigators must be aware of the size and posterior situation of the cartilaginous septum in order to suture stents of correct size onto the septum.

Interestingly, despite the difference in head size, the frontal sinus ostia in all 4 swine head were around 10 cm from the nasal aperture. In the domestic swine this meant that the frontal sinus ostia are easily accessible using standard 0-degree endoscopes and sinus instruments. This is an obvious advantage over previous sheep models where standard instrumentation could not reach the sinuses. The swine model allows access to the frontal sinus for placement of topical medication. Furthermore, silastic splints can be

securely sutured to the nasal septum through the posterior cartilaginous part. This would allow us to study the safety and efficacy of medications, such as fucoidan, incorporated within the silastic splints on the nasal mucosal membrane. The domestic swine, therefore, meets the anatomic feasibility criteria we set out at the start of the study, making it a suitable animal model to study the effects of topical medications on sinonasal mucosal wound healing. However, the nasal cavities of the Yucatan miniature swine were too small to allow for endoscopy, access to the frontal sinus or suturing of silastic splints to the septum. The Yucatan miniature swine thus does not meet the anatomic feasibility criteria, making them unsuitable for our purposes of applying medications to the frontal sinus in the future. However, the Yucatan miniature pigs may still be a feasible animal model for other studies in which the size of the nasal cavity does not become an issue. For example, research in cranial facial surgeries implement the Yucatan miniature pig sinuses as models and gain access through direct opening of the sinuses.^{26,27} Thus, investigators must consider the feasibility of using other methods to access the sinuses of the domestic and Yucatan swine if not using an endoscopic approach.

Interpretation in relationship to current literature

To our knowledge, this is the first project to investigate and correlate the CT and endoscopic anatomy of the domestic and Yucatan swine in order to determine their feasibility as animal models for studies of medications delivered via FESS. As such, the study provides timely, original, and worthwhile addition to the current literature on the use of swine paranasal sinuses as animal models.


Limitations of the study and future direction

A limitation of this study is that a small number of domestic and Yucatan pigs were used for endoscopy. A larger sample size would be required for more extensive comparisons between swine class. Also, the information provided in this work, such as the sizes of the frontal sinuses and cartilaginous nasal septum, can serve as initial information that future studies can build upon. With an increase in a number of animals studied, it is possible to eventually attain an average size of frontal sinuses and cartilaginous nasal septum by polling the results of the present and future studies together.

In our study, the domestic swine used were 6 months old. It would be interesting to find out the minimal age at which the nasal cavities of the domestic swine grow to a size large enough to accommodate endoscopic maneuvers. This information, combined with the maximal size of domestic swine that an institution can accommodate in its animal care facility, will provide investigators further information about how long they can study the animals, and is crucial in the planning of experiments.

Conclusion

Both domestic and Yucatan miniature swine nasal sinus anatomy is similar to that of human anatomy. The domestic swine can be used as an animal model to study the effect of topical medications on sinonasal mucosal wound healing delivered using standard FESS instruments for a number of reasons. First, the sinus anatomy is similar to that of humans. Second, their frontal sinuses can be readily accessed with greater ease than those of humans due to their position in the horizontal plane in relation to the snout, using standard endoscopic sinus instruments for depositions of medications. Finally, the posterior cartilaginous septum provides

an area of nasal mucosa onto which drug-embedded stents can be sutured easily. On the other hand, the Yucatan pigs were not suitable animal models for future investigations of medications delivered using standard FESS instruments due to their narrow nasal cavities. 

Acknowledgements

We acknowledge and thank Stephanie Smith and Jae Lee for their help in obtaining domestic and Yucatan pig heads for our study. Also, we acknowledge the help of Rachele (Dar Santos) Moshfeghi, our clinical research coordinator, for making the logistics of the research project possible.

References

1. Chow PKH, Ng RTH, Ogen BE. Using animal models in biomedical research—a primer for the investigator. Singapore: World Scientific Publishing Co.; 2008.
2. Cashman JD, Kennah E, Shuto A, Winternitz C, Springate CMK. Fucoidan film safely inhibits surgical adhesions in a rat model. *J Surg Res*. 2011;171:495–503.
3. Li PM, Downie D, Hwang PH. Controlled steroid delivery via bioabsorbable stent: safety and performance in a rabbit model. *Am J Rhinol Allergy*. 2009;23:591–596.
4. Maccabee MS, Trune DR, Hwang PH. Effects of topically applied biomaterials on paranasal sinus mucosal healing. *Am J Rhinol*. 2003;17:203–207.
5. Proctor M, Proctor K, Shu XZ, McGill LD, Prestwich GD, Orlandi RR. Composition of hyaluronan affects wound healing in the rabbit maxillary sinus. *Am J Rhinol*. 2006;20:206–211.
6. Ingrams DR, Volk MS, Biesman BS, Pankratov MM, Shapshay SM. Sinus surgery: does mitomycin C reduce stenosis? *Laryngoscope*. 1998;108:883–886.
7. Rahal A, Peloquin L, Ahmarani C. Mitomycin C in sinus surgery: preliminary results in a rabbit model. *J Otolaryngol*. 2001;30:1–5.
8. Maccabee MS, Trune DR, Hwang PH. Paranasal sinus mucosal regeneration: the effect of topical retinoic acid. *Am J Rhinol*. 2003;17:133–137.
9. Hwang PH, Chan JM. Retinoic acid improves ciliogenesis after surgery of the maxillary sinus in rabbits. *Laryngoscope*. 2006;116:1080–1085.
10. Gardiner Q, Oluwole M, Tan L, White PS. An animal model for training in endoscopic nasal and sinus surgery. *J Laryngol Otol*. 1996;110:425–428.
11. Swibel-Rosenthal LH, Benninger MS, Stone CH, Zacharek MA. Wound healing in the paranasal sinuses after coblation, part II: evaluation for endoscopic sinus surgery using a sheep model. *Am J Rhinol Allergy*. 2010;24:464–466.
12. Shaw CL, Dymock RB, Cowin A, Wormald PJ. Effect of packing on nasal mucosa of sheep. *J Laryngol Otol*. 2000;114:506–509.
13. McIntosh D, Cowin A, Adams D, Wormald PJ. The effect of an expandable polyvinyl acetate (Merocel) pack on the healing of the nasal mucosa of sheep. *Am J Rhinol*. 2005;19:577–581.
14. Rajapaksa S, McIntosh D, Cowin A, Adams D, Wormald PJ. The effect of insulin-like growth factor 1 incorporated into a hyaluronic acid-based nasal pack on nasal mucosal healing in a healthy sheep model and a sheep model of chronic sinusitis. *Am J Rhinol*. 2005;19:251–256.
15. Rajapaksa SP, Cowin A, Adams D, Wormald PJ. The effect of a hyaluronic acid-based nasal pack on mucosal healing in a sheep model of sinusitis. *Am J Rhinol*. 2005;19:572–576.
16. Robinson S, Adams D, Wormald PJ. The effect of nasal packing and prednisolone on mucosal healing and reciliation in a sheep model. *Rhinology*. 2004;42:68–72.
17. Stelzle F, Benner KU. An animal model for sinus floor elevation with great elevation heights. Macroscopic, microscopic, radiological and micro-CT analysis: *ex vivo*. *Clin Oral Implants Res*. 2010;21:1370–1378.
18. Jarraya R, Young J, Berci G, Shahinian HK. Endoscopic skull base surgery I: a new animal model for pituitary surgery. *J Invest Surg*. 1999;12:289–294.
19. Mladina R, Vuković K, Štern Padovan R, Skitarelić N. An animal model for endoscopic endonasal surgery and dacryocystorhinostomy training: uses and limitations of the lamb's head. *J Laryngol Otol*. 2011;125:696.
20. Briner HR, Simmen D, Jones N, et al. Evaluation of an anatomic model of the paranasal sinuses for endonasal surgical training. *Rhinology*. 2007;45:20–23.
21. Larjava H, Wiebe C, Gallant-Behm C, Hart D, Heino J, Häkkinen L. Exploring scarless healing of oral soft tissues. *J Can Dent Assoc*. 2011;77:b18.
22. Wadell C, Bjork E, Camber O. Permeability of porcine nasal mucosa correlated with human nasal absorption. *Eur J Pharm Sci*. 2003;18:47–53.
23. Vodička P, Smetana K, Dvořánková B, et al. The miniature pig as an animal model in biomedical research. *Ann N Y Acad Sci*. 2005;1049:161–171.
24. Nunoya T, Shibuya K, Saitoh T, et al. Use of miniature pig for biomedical research, with reference to toxicologic studies. *J Toxicol Pathol*. 2007;20:125–132.
25. Becker SS. Preoperative computed tomography evaluation in sinus surgery: a template-driven approach. *Otolaryngol Clin North Am*. 2010;43:731–751.
26. Lenz J, Henkel K, Schmidt W, Fulda G, Hingst V, Gundlach KKH. Ossification of the frontal sinus in juvenile minipigs following water jet application. *J Craniomaxillofac Surg*. 2006;34:93–99.
27. Gruber RM, Ludwig A, Merten HA, Pippig S, Kramer FJ, Schliephake H. Sinus floor augmentation with recombinant human growth and differentiation factor-5 (rhGDF-5): a pilot study in the Goettingen miniature pig comparing autogenous bone and rhGDF-5. *Clin Oral Implants Res*. 2009;20:175–182.