Computed Axial Tomography of the Porcine Nasal Cavity and a Morphometric Comparison of the Nasal Turbinates with Other Visualization Techniques

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ABSTRACT

A non-invasive imaging modality, computed tomography (CT), was used to visualize changes in nasal turbinates of anesthetized pigs over a 12-week observation period (pigs were 14 wk of age at study week 0). Normal, non-infected pigs were compared to pigs with mild challenge-induced atrophic rhinitis (AR) in order to detect subtle differences in morphology. To determine feasibility for time course studies in future experiments, morphometric quantitation at the level of the 2nd premolar (turbinate area ratio or TAR) in cross-section CT images at multiple timepoints was done. Additionally, at study termination, the TAR determined from CT images, magnetic resonance imaging (MRI), and wet tissue (WT), were compared to each other and to the standard subjective measure, visual scoring.

There were no statistically significant differences between the control and AR groups at CT imaging dates of 0, 3, 6, 9, or 12 wk (P = 0.182). However, a statistically significant decrease in TAR measurements over time (P = 0.015) was observed in both groups, with lower mean values observed on Weeks 3 and 6 before rebounding to baseline values at study termination. At Week 12 (termination of the study), the TAR measurements derived from CT, MRI, and WT were not statistically different from one another (P = 0.220) and the treatment group-by-method interaction was not significant (P = 0.800). This provided evidence of equivalency of the techniques. Mean values for normal and infected groups were not significantly different based on either TAR imaging methods (P = 0.552) or visual scores (P = 0.088).

Thus, the current study demonstrated that CT was an acceptable alternative imaging modality which could be used for quantitation of turbinate changes in snouts of live pigs to provide data comparable to tissue taken at necropsy. Computed tomographic imaging would allow non-invasive tracking of disease or treatment responses within individual animals over time. Morphometric analysis of the TAR was equivalent between the CT, MRI, and WT specimens.

INTRODUCTION

Atrophic rhinitis (AR) in swine is associated with *Pasteurella multocida* type D (toxigenic) and *Bordetella bronchiseptica* which progressively results in mild to severe anatomical deformation of the snout (1,2). The nasal septum may become thickened and malaligned while the turbinates may become atrophied. Various morphometric techniques have been applied to quantitate the changes in nasal architecture that are associated with AR, usually measured on a cross-sectional slice of the snout at the level of the 2nd premolar. Generally, the turbinate perimeter ratio and the turbinate area ratio along with the septum score are determined (3,4). Therefore, in longitudinal studies of AR, it has been necessary to use large numbers of pigs because several animals must be euthanized at selected timepoints in order to obtain the cross-sectional snout slices needed to perform the evaluations. Because of the expense and welfare issues surrounding the need to use large numbers of pigs for these studies, it would be desirable to have an alternative antemortem procedure available that could minimize the use of animals yet provide valid data to the investigator. Computed tomography (CT) has been well documented in man for otolaryngological use in patients (5) and has also been applied in a preliminary research situation to the pig (6,7). The basic principle behind CT is that the internal shape of a structure or object in vivo can be reconstructed or "imaged" from multiple projections of that object (8). The nasal cavity and paranasal sinuses in mammals have air, soft tissue and mineral opacities and thus differing contiguous linear attenuation coefficients. These differing linear attenuation coefficients allow optimally enhanced visualization of contiguous structures. Volumes of tissue irradiated in CT are considerably smaller in volume than those used in conventional X-rays, resulting in optimal contrast due to less scattered X-ray photons. Magnetic resonance imaging (MRI) is another

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non-invasive technique commonly employed in human medicine (9). It uses non-ionizing radiation which can differentiate between different types of tissues due to differences in structure and water content. MRI uses a radio frequency to stimulate a tissue itself to produce a signal. Compact bone gives no signal in MRI, and therefore no signal is seen in the regions of the calvarium, petrous ridges and orbital bones. However, soft tissues such as the turbinate lining are easily examined using MRI. The purpose of the present experiment was to evaluate computed tomography (CT), a non-invasive imaging modality, to track the morphological changes in the nasal cavity of pigs over a 12-week period, and then at necropsy, to compare the morphometric analysis of CT and MRI images to wet tissue and to a traditional visual lesion scoring system for the same cross-sectional snout slice.

MATERIALS AND METHODS

ANIMALS

Twelve specific pathogen free (SPF), Landrace-Large White cross piglets from a totally confined secondary SPF swine herd were weaned 3 wk postpartum. To minimize confounding results from extraneous respiratory pathogens in this study, each piglet received 2.5 mg/kg of the antibiotic enrofloxacin (Baytril, Miles Inc., Shawnee Mission, Kansas, USA) intramuscularly for 3 consecutive days preweaning. After weaning, piglets were water medicated with 180 ppm tiamulin (Denagard, Fermenta Animal Health, Kansas City, Missouri, USA) for 5 d. At 7 wk of age, piglets were randomly selected from the herd and housed in 3 isolation rooms measuring 1.49 m^2 for the duration of the study. Four pigs were maintained as control pigs in a room separate from the the other 8 which were challenged intranasally with a combination of *P. multocida* and *B. bronchiseptica*. Feed consisted of 2–3 kg ground corn-soy diet (14% crude protein) per day. Imaging was initiated at 14 wk of age (the $\bar{x}$ weight = 45 kg).

ANIMAL CARE

Daily clinical examinations were conducted on the pigs and included observation for any signs of disease or abnormal physiology or feces, as well as feed intake measurements. Pigs were weighed on the days that they were imaged (no performance data were calculated due to the small numbers of pigs used). On the last date of imaging, the pigs were euthanized with supersaturated sodium pentobarbital after image acquisitions.

MICROBIOLOGY

Bacterial inoculation culture preparation was done using procedures similar to those previously described (3). Four mL/naris of a combination of *P. multocida* 10103 (9×10^9 cfu/mL) and *B. bronchiseptica* 155D (8×10^7 cfu/mL) were instilled into each 14-week-old pig subsequent to the Week 0 imaging.

Microbiological sampling was conducted on the pigs at 7, 14, 17, 20, 23, and 26 wk of age. During anesthesia, the nasal orifice was cleansed of mucus and debris with a sterile alcohol moistened gauze pad, then a thioglycolate broth-moistened cotton swab was inserted into the nares of each pig. Upon withdrawal, the tip was swabbed onto 5% sheep blood and MacConkey agar plates, then deposited into a tube of thioglycolate medium. The plates were incubated at 37°C in 6.9% CO_2, and examined for growth at 24 and 48 h. Thioglycolate broth incubated at 37°C overnight was subcultured onto agar as above. Isolated bacteria were identified by colonial morphology, Gram stain, API20E (bioMerieux Vitek, Hazelwood, Missouri, USA) and MiniTek (Becton Dickinson Microbiology Systems, Cockeysville, Maryland, USA).

ACQUISITION OF CT IMAGES

On the day of imaging, each pig was anesthetized with a mixture of equal parts per volume of ketamine (Ketaset, Fort Dodge Laboratories, Fort Dodge, Iowa, USA) xylazine (Rompun, Haver Diamond Scientific, Shawnee Mission, Kansas, USA) zolazapam and tiletamine (Telazol, Fort Dodge Laboratories, Fort Dodge, Iowa, USA) injected intramuscularly at a rate of 1cc/22.7 kg (50 lb) for intubation. Pigs were maintained on halothane at 2% with 2 L O_2/min. Following an accidental death of 1 pig at study Week 6, a rigid oral speculum was subsequently used to prevent the weight of the animal's mandible from collapsing the anesthetic endotracheal tube.

Computed tomographic images of all pigs were acquired at 14, 17, 20, 23 and 26 wk of age (study Weeks 0, 3, 6, 9, and 12) using a General Electric CT/T 8800 computed axial tomograph (General Electric Medical Systems, Milwaukee, Wisconsin, USA). Non-infected pigs were imaged prior to the infected pigs to avoid cross-contamination. A marker (tattoo) was placed on the gum line of each pig to serve as a standard marker for alignment consistency at each imaging date. Slice thickness and spacing for axial (transverse) slices were 5 mm. Slices were made from the os rostrale bone caudally to and including the entire nasal cavity and paranasal sinuses (however, for morphometric analyses, only the slice at the level of the 2nd premolar was evaluated). A window width (contrast) of 2000 was used for all CT images for optimal resolution. The window level (brightness) varied depending on the anatomical area of interest. Images were acquired using the bone algorithm and took approximately 60 min for each animal. Each computed image was transferred to hard copy film utilizing a format camera (Matrix Camera, MI-10, Matrix Instruments, Orangeburg, New York, USA).

ACQUISITION OF MR IMAGES

At study Week 12 (26-week-old pig), MR images were acquired on each pig while maintaining the anesthesia established for CT imaging. A fat capsule marker was used to calibrate the slice image so that the 2 imaging modalities could be compared. Images were acquired with a 12.7-centimetre surface coil in a 0.15T Technicare (Solon, Ohio, USA) whole body imager utilizing a multi-slice, spin-echo (SE) technique with a repetition time of 800 ms (TR) and an echo time of 30 ms (TE). Transverse contiguous slices of 5 mm were made, with 5 rostral to and 5 caudal to the 2nd upper premolar tooth. Only images at the level of the 2nd premolar were used in morphometric analyses. Image acquisition took approximately 30 min for each animal. Each computed image was transferred to hard copy film utilizing a format camera.

MORPHOLOGY OF CT IMAGES OVER TIME

On each image date, the size, shape, symmetry and opacities of the nasal cavity and paranasal sinuses were subjectively evaluated, whereas the images captured at 12 wk were compared to necropsy specimens collected from the same anatomical region as the CT images.

MORPHOLOGY OF MR IMAGES

Magnetic resonance images captured at 12 wk were compared to necropsy specimens collected from the same anatomical region as the CT images.

COLLECTION OF SNOUT SECTIONS

A 1-centimetre transverse section was taken from euthanized pigs immediately rostral to the 2nd premolars and stored in 10% buffered formalin. Section location was critically maintained because the size of the turbinate bone diminishes rostrally and measurements or scoring may not be valid if the section is inaccurately obtained (10).

VISUAL SNOUT SCORING

Visual scoring is the current "standard" in grading morphological snout alterations in swine atrophic rhinitis. Each snout was visually scored independently by 9 individuals. Left and right turbinate atrophy and deviation of the nasal septum were each graded separately on a scale of 0 to 3; normal turbinate scrolls or septum received a grade of 0; slight, moderate and severe atrophy of the dorsal or ventral portions of the scrolls, or deviation of the septum, were graded as 1, 2 and 3, respectively. The 3 scores from each snout were then added together and divided by 3. Thus, total scores for each pig could range from 0 to 3. The total score for each pig was determined and a group mean calculated.

SNOUT PHOTOGRAPHY

Color photographs of wet tissue were used for a reference when tracing images for morphometric evaluation or verification of statistical outliers.

IMAGE COLLECTION

Images of sections of pig snouts (wet tissue) were digitized using Colorkit software (Data Translation, Marlbora, Massachusetts, USA) on a Macintosh Quadra 700 (Apple Computer, Cupertino, California, USA) microcomputer linked to a color video camera (Chromachip II, Javelin Electronics, Torrance, California, USA) mounted over a lightbox. An image of a ruler was captured for calibration. Images were stored on optical disk. Images of CT and MRI films were evaluated by laying the film directly on the lightbox and digitizing an image with the same software and hardware described above. An image of the ruler was also captured for calibration of both CT and MRI images.

SNOUT MORPHOMETRY

Morphometric evaluations were made on pig snout images from CT films, MRI films and wet tissue (WT) at study week 12. Computed tomography evaluations were made at 3-week intervals from 0 through 12 wk to assess the comparability of results at different time points. Morphometric evaluation was performed using NIH Image 1.47 software (Wayne Rasband, National Institutes of Health, Bethesda, Maryland, USA) on a Macintosh computer. The freehand tool was used to trace first the nostril area, and then the turbinate area. Dorsal conchae were excluded from measurement using the method of Gatlin, et al (3), which is a modification of the method established by Collins, et al (4). All measurements were electronically copied to a spreadsheet for calculation and evaluation. Turbinate area ratio (TAR) was calculated by dividing the turbinate area by the nostril area.

STATISTICAL ANALYSIS

A mixed effects repeated measures model was used to analyze the longitudinal turbinate area ratio (TAR) values determined by the CT method at 3-wk intervals. The main effects and interaction of Treatment Group and Week were defined as fixed effect factors in the analysis of variance (ANOVA) model, and Animal within Treatment Group was defined as a random effect. Observations between animals were considered independent, and measurement errors within an animal were assumed independent across weeks.

A mixed effects repeated measures model was also used to analyze the MRI, CT, and WT determinations of TAR values at 12 wk post-treatment. The main effects and interaction of Treatment Group and Imaging Method were defined as fixed effect factors in the model, and Animal within Treatment Group was defined as a random effect. Observations between animals were considered independent, and an unstructured covariance structure was assumed between the 3 determinations for an animal.

Statistical significance of the fixed effects factors in the ANOVA model were tested at the nominal 0.05 level using the approximate F-tests computed by the Mixed Procedure in SAS/STAT Software (11).

Statistical significance of the difference in mean visual scores for control and challenged animals was tested using the nonparametric Wilcoxon rank sum test available within JMP Statistical Discovery Software (12). Linear associations among the morphometric TAR measurements were examined using a scatterplot matrix and Pearson's product moment correlations. Kendall's tau-b was computed as a nonparametric measure of association between TAR measurements and visual score.

RESULTS

ANIMAL HEALTH

All challenged animals experienced anorexia for 2 to 3 d with sneezing in some pigs; non-infected pigs remained normal. The health status of all the pigs remained normal for the duration of the trial as judged by daily physical examination. Thus, from a clinical perspective there was no evidence of AR in the challenged pigs. Bacteriological monitoring of the challenged pigs during each imaging did not result in consistent recovery of *P. multocida* or *B. bronchiseptica*. The control pigs had no culture positive isolations consistent with the challenge strains.

One pig was euthanized for welfare reasons after the 2nd imaging due to the detection of a large demarcated mass impinging on the trachea. This mass was diagnosed as an advanced lymphosarcoma and was considered an incidental finding in regard to this study. One pig died during the 3rd imaging due to asphyxiation caused

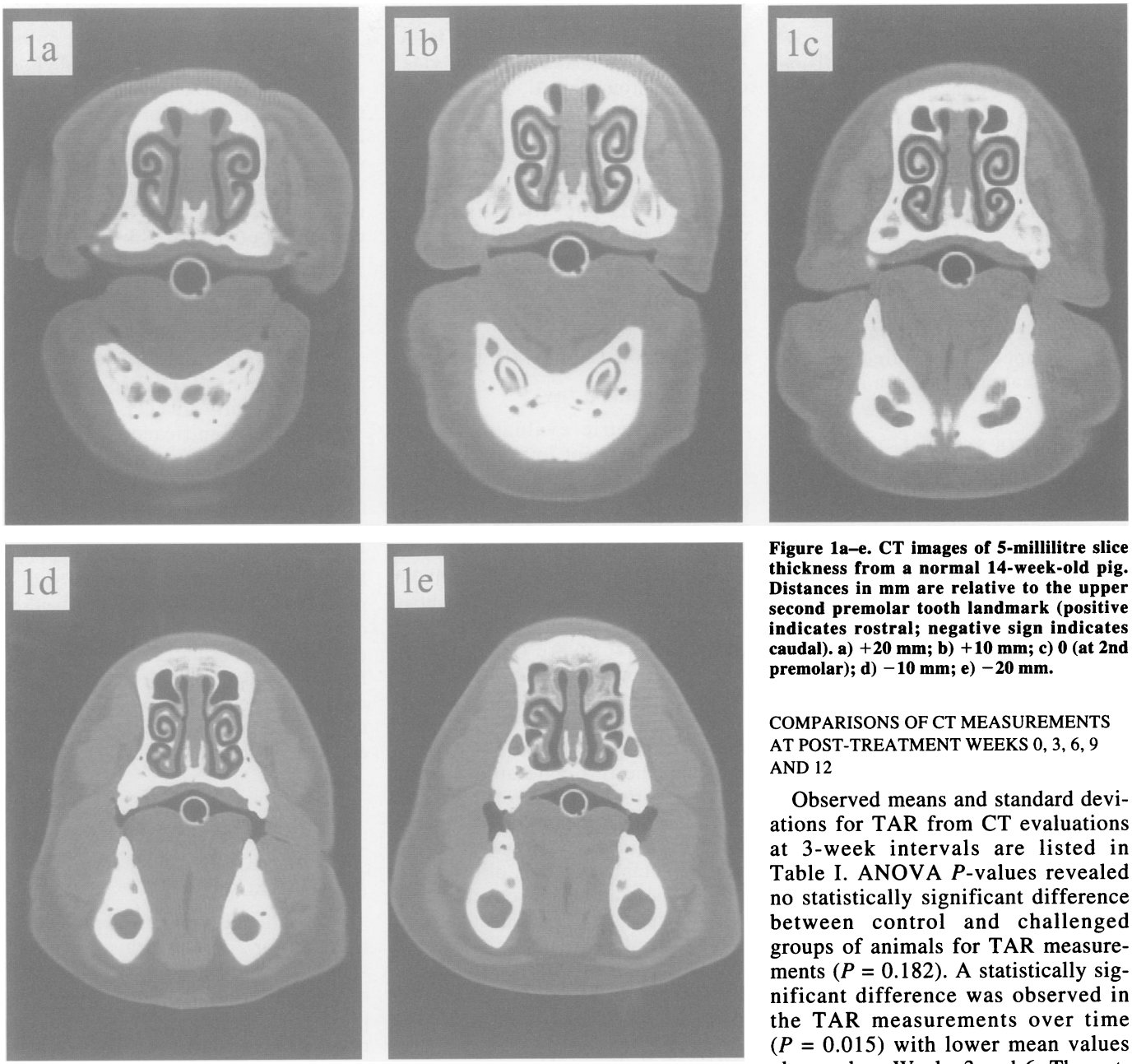


Figure 1a–e. CT images of 5-millilitre slice thickness from a normal 14-week-old pig. Distances in mm are relative to the upper second premolar tooth landmark (positive indicates rostral; negative sign indicates caudal). a) +20 mm; b) +10 mm; c) 0 (at 2nd premolar); d) −10 mm; e) −20 mm.

by restriction of the endotracheal tube and was considered an accidental death. Feed intake and feces appeared normal throughout the study. The average weight of the pigs at 26 wk was 110 kg.

MORPHOLOGY OF CT IMAGES

Figure 1 is comprised of 5 CT images from the same normal animal at week 0 beginning −20 mm ventrally from the 2nd premolar and sequentially proceeding caudally in 10 mm "slices" to +20 mm from the 2nd premolar. Typical anatomical structures were identified from the images, and the endotracheal tube was visible as a ring in each image. The best cross-sectional location to quantify turbinate size was at the 2nd premolar.

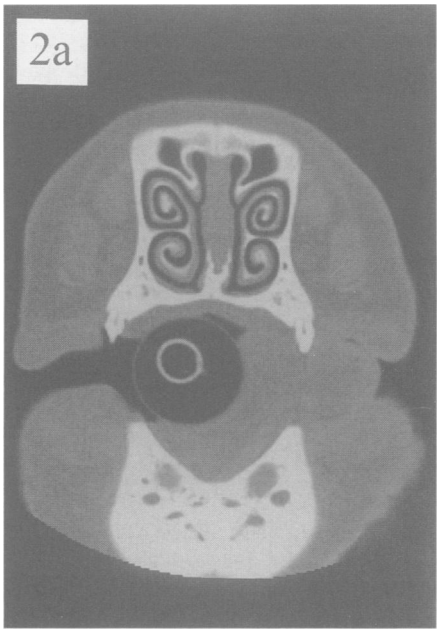
Figure 2 compares CT to MR images of a single normal pig on the same day. In the CT image (Fig. 2a), image intensity for mineralized tissues is strong while soft tissues are less prominent. In contrast, note the increased intensity of soft tissues and decreased prominence of mineralized tissues in the MR image. In the MR image, decreased dorsal to ventral image intensity was due to use of a surface receiver coil (a circumferential or volume coil would have produced a relatively uniform gauge intensity, but was not available for this experiment).

COMPARISONS OF CT MEASUREMENTS AT POST-TREATMENT WEEKS 0, 3, 6, 9 AND 12

Observed means and standard deviations for TAR from CT evaluations at 3-week intervals are listed in Table I. ANOVA *P*-values revealed no statistically significant difference between control and challenged groups of animals for TAR measurements ($P = 0.182$). A statistically significant difference was observed in the TAR measurements over time ($P = 0.015$) with lower mean values observed on Weeks 3 and 6. The pattern in mean response across weeks was similar between control and challenged animals as evidenced by an ANOVA *P*-value for Experimental Group-by-Week interaction equal to 0.080 for TAR. The response pattern for TAR was characterized by the least-squares-means.

COMPARISONS AT 12 WEEKS

Summarized morphometric evaluations and visual scores at 12 wk for control and challenged groups are listed in Table II. Of the 10 pigs graded at necropsy by visual scoring, 5 were completely normal (score 0-including all 3 control pigs), 4 were categorized as normal although some



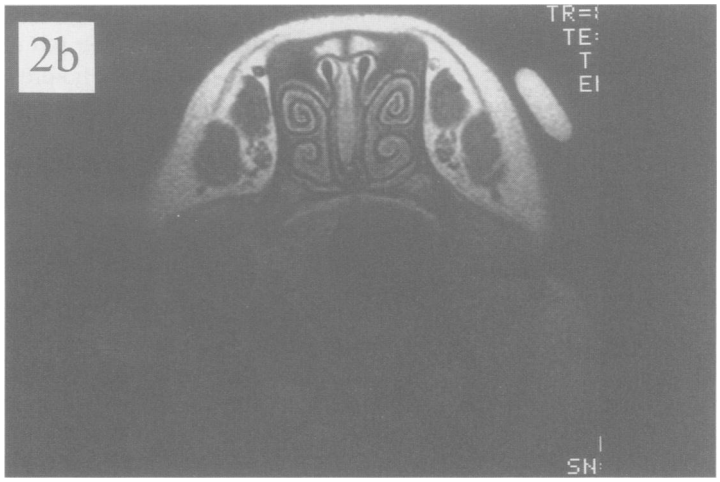


Figure 2a,b. CT (a) and MR images (b) of a normal snout from a 26-week-old pig at the 2nd premolar. Contrast strong image intensity of mineralized tissues in the CT image to strong image intensity of soft tissues, especially fat, in the MR image.

abnormality was observed (score range 0.33–1), and 1 pig was slightly affected (score 1.67). The mean scores for control and challenged pigs were not significantly different from one another ($P = 0.088$).

The analysis of TAR measurements revealed no statistically significant mean differences between control and challenged groups of animals ($P = 0.552$) or between morphometric methods ($P = 0.220$), with a non-significant Treatment Group-by-Method interaction ($P = 0.800$). These results are consistent with previous tests for treatment effects based on analysis of longitudinal CT measurements ($P = 0.182$) and visual scores (0.088). However, the smaller P-value for visual scores suggests that the traditional method may be more sensitive than either wet tissue or morphometric analysis of CT and MRI images in evaluating changes in nasal turbinates.

Linear measurements of association are summarized in Table III. Coefficients are generally less than 0.5 in absolute value, suggesting a weak correlation among the 4 methods of evaluation. Morphometric measurements are negatively correlated with visual score, with the highest correlations for CT evaluations (−0.536). Caution is needed in interpreting these associations, however, because the limited number of pigs make the correlation coefficients in the table unreliable.

TABLE I. Observed turbinate area ratio (TAR) means and standard deviations in computerized axial tomography images acquired over 12 wk

		Observation week				
Group		0	3	6	9	12
Control	$\bar{x}$	0.420	0.315	0.397	0.443	0.430
	s[a]	0.076	0.049	0.035	0.065	0.044
	n	4	4	3	3	3
Challenged	$\bar{x}$	0.405	0.360	0.300	0.351	0.393
	s	0.040	0.080	0.089	0.076	0.045
	n	8	8	7	7	7
Combined	$\bar{x}$	0.410	0.345	0.329	0.379	0.404
	s	0.052	0.072	0.088	0.083	0.046
	n	12	12	10*	10	10

[a] s: standard deviation
* Two animals were removed from study

TABLE II. Observed turbinate area ratio (TAR) means and standard deviations evaluations at 12 wk

		TAR values			
		MRI	CT	WT	VS
Control	$\bar{x}$	0.440	0.430	0.403	0.000
($n = 3$)	s[a]	0.072	0.044	0.021	0.000
Challenged	$\bar{x}$	0.436	0.393	0.384	1.714
($n = 7$)	s	0.078	0.045	0.068	1.799
Combined	$\bar{x}$	0.437	0.404	0.390	1.200
($n = 10$)	s	0.072	0.046	0.057	1.687

[a] s: standard deviation
MRI = Magnetic resonance imaging
CT = Computed axial tomography
WT = Wet tissue
VS = Visual score

DISCUSSION

The length of the porcine nasal cavity, presence of air, soft tissue and mineral opacities and morphological structure of the paranasal sinuses permit ideal image resolution with CT. MR imaging contrast is primarily due to the water content of the tissue. While CT and MRI are not economically feasible to use in the marketing field for determining disease states in swine, they would be useful research tools for following treatment response

TABLE III. TAR values correlation coefficients* evaluations at 12 wk in normal to mildly affected pigs

	CT	MRI	WT	VS
CT	1.000	0.367	0.323	−0.591
MRI	0.367	1.000	0.490	−0.407
WT	0.323	0.490	1.000	−0.720
VS	−0.591	−0.407	−0.720	1.000

TAR = Turbinate area ratio
MRI = Magnetic resonance imaging
CT = Computed axial tomography
WT = Wet tissue
VS = Visual score
* All coefficient correlations were evaluated using Pearson product moment except VS, which used Kendall's tau-b

of swine in diseases such as atrophic rhinitis. Severe pathologic changes of the nasal cavity must occur to be seen on conventional radiography. Computed tomography can be used to detect much more subtle changes than conventional radiography due to small slice thickness that results in enhanced image contrast. Also, acquisition of image data is parallel to the X-ray beam rather than perpendicular to it, resulting in additional morphological information relative to conventional radiography. Therefore, diseases such as atrophic rhinitis in swine can be investigated with these non-invasive procedures. There has been very little published literature on the investigation of turbinate changes in the porcine nasal cavity using CT or MRI (6,7).

In systems without motion or flow, the signal intensity of MR images is dependent on 3 variables (T_1, T_2 and proton density) as opposed to the single variable in CT (attenuation coefficient) (9). Contrast between tissues in the image can be influenced by altering individual pulse sequences, thus high-lighting any 1 of the 3 parameters. However, a multiplicity of sequences will prolong acquisition time. The availability of direct sagittal and dorsal imaging allows very accurate and rapid localization of nasal pathology without the relatively high radiation dose.

CT images of 14-, 17-, 20-, 23- and 26-week-old pigs were compared to swine nasal anatomy described in textbooks (1,10,13–15) . A good visual correlation exists among normal gross specimens, computed images, and textbook anatomy. The slight atrophic rhinitis in the infected pigs gave investigators some turbinate changes to evaluate, as a means to test the level of sensitivity of the measurement. The fact that bacteriological cultures were predominantly negative for the challenge organisms supports the clinical observation of a less severe AR.

The CT slice thickness of 5 mm provided good resolution. Optimal resolution might be obtained by localizing the anatomical section of the nasal cavity (maxillary 1st and 2nd premolar area) and obtaining 1.5-millimetre slices instead of 5-millimetre slices. The resolution in the MRI was not as good due to the coil size and shape which was not adequately designed to encompass the snout anatomy.

The statistically significant difference in mean CT images and TAR response at Weeks 3 and 6 in may have been due, in part, to the location of imaging at each timepoint. It was easy to consistently slice the wet tissue in the same location for each pig, whereas it was more difficult to determine the exact location at each timepoint and from pig to pig with the non-invasive imaging modalities. The angle of image acquisition (variation from perpendicular) can affect mensuration data. TAR ratios varied from week to week, but returned to nearly the same value by study Week 12 as Week 0.

The current study indicates that CT (and MRI when coil design is optimized) has the potential to be an acceptable alternative technique to visual lesion scoring of wet tissue which can be used for non-invasive, antemortem quantitation of turbinate changes in an individual pig. This could be of use in studies of pathogenesis of AR, or anti-infective evaluations that require a longitudinal tracking of disease or treatment responses within a single animal.

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