








Original Article

Association of Lymphatic Fluid Volume in the Inner Ear of Beagle Dogs with the Susceptibility to Motion Sickness

Mingliang Cai^{1*} , Lei Cui^{2*} , Junfeng Xu² , Lihua Xu¹ , Chang Ren¹ , Xin Zhou¹ , Zhenglin Jiang¹ 

¹Department of Neurophysiology and Neuropharmacology, Institute of Special Environmental Medicine, Institute of Nautical Medicine, Nantong University, Nantong, Jiangsu, China

²Department of Radiology, Affiliated Hospital 2 of Nantong University, Nantong, Jiangsu, China

ORCID IDs of the authors: M.C. 0000-0002-2317-7373, L.C. 0000-0001-7763-5205, J.X. 0000-0002-0866-144X, L.X. 0000-0002-3027-2483, C.R. 0000-0002-5145-6409, X.Z. 0000-0002-8851-9995, Z.J. 0000-0002-7134-5511.

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BACKGROUND: This study aimed to quantify total lymphatic fluid spaces of the inner ears volumetrically in the dog in order to find a correlation between the lymphatic volume of the inner ears and motion sickness susceptibility.

METHODS: A total of 16 healthy adult Beagle dogs were used to delineate the lymphatic fluid spaces of inner ears by magnetic resonance imaging with a 3-dimensional-constructive interference steady-state sequence. Manual segmentation was applied for 3-dimensional reconstruction and volumetric quantification of total lymphatic space. The susceptibility of Beagle dogs to motion sickness was judged by latency of vomiting during rotatory stimulus.

RESULTS: The volume range of total fluid space in the vestibule and cochlea of Beagle dogs is $55.07 \pm 6.2 \text{ mm}^3$. There is no significant difference in the total lymphatic volume of bilateral inner ears between 2 different motion sickness susceptibility groups (i.e., sensitive group and insensitive group), but the difference of lymphatic volume in the cochlea and vestibule between bilateral inner ears in insensitive group is greater than that of sensitive group. Moreover, a significant positive correlation was found between bilateral inner ear difference in lymphatic volume and vomiting latency.

CONCLUSION: Magnetic resonance imaging could be used as a method to evaluate the inner ear lymphatic fluid volume of Beagle dogs with different susceptibilities to motion sickness, through which we found that motion sickness susceptibility is related to the difference in lymphatic volume in the vestibule and cochlea between bilateral inner ears, and the larger the volume difference, the lower the susceptibility.

KEYWORDS: Motion sickness, Beagle dogs, inner ear, MRI, lymphatic volume

INTRODUCTION

Motion sickness can be caused by a variety of motion environments (e.g., cars, boats, planes, tilting trains, funfair rides, space, virtual reality).¹⁻³ Almost everybody will experience motion sickness at least once in his/her lifetime.¹⁻³ Motion sickness can develop in any individual if the movements applied to the body are significant enough.¹ However, there are considerable individual differences in the susceptibility to motion sickness, which might be a result of gene-environment interaction.^{1,2} Young people, especially children between the ages of 6-12 years, and women are believed to be more sensitive to motion sickness.⁴⁻⁶

The theory of sensory conflict and neural mismatch is the most widely accepted theory to explain motion sickness.^{1,2,6,7} When there is a discrepancy between actual versus expected patterns of vestibular, visual, and kinesthetic inputs, it initiates the cascade of motion sickness symptoms.^{1,2} One of the situations is that the information upload from asymmetric otolith organs leads to signal conflicts and causes motion sickness.^{6,8,9}

*MC, and LC contributed equally to this work.

Corresponding author: Xin Zhou, e-mail: zhouxin2046@126.com

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When given a sufficiently provocative motion stimulus, almost anyone with a functioning vestibular system can be made motion sick.¹ People with complete loss of vestibular function are immune to motion sickness, and those with half-loss of vestibular function are less likely to be affected than normal people.¹⁰ Therefore, motion sickness susceptibility can be linked to vestibular function.

The vestibular system is responsible for equilibrioception, including detection of motion and positional changes, sense of balance, and spatial orientation.¹¹ The structural integrity of the inner ear and homeostasis of the endolymph and perilymph are essential for the maintenance of vestibular function. The homeostasis of endolymph plays an important role in vestibular sensation.¹² When the head moves, the endolymph fluid will push the hairy protrusions in a specific direction, causing the hair cells to be excited to sense changes in the direction of movement. When the endolymphatic ducts are blocked, the reabsorption of endolymph fluid will decrease, resulting in the accumulation of water in the labyrinth.¹²⁻¹⁴ It will evoke vestibular autonomic reactions with symptoms similar to motion sickness (pale, sweating, dizziness, nausea, vomiting, etc.).^{14,15} However, it is unclear whether the inner ear lymphatic fluid volume is linked to motion sickness susceptibility. In this study, we hypothesized that there were differences in lymphatic volume among individuals with different susceptibilities to motion sickness. Therefore, the present study was designed to investigate the relationship between the lymphatic volume measured with magnetic resonance imaging and motion sickness susceptibility in the dog to uncover inner ear-related mechanism of motion sickness.

MATERIALS AND METHODS

Animals and Ethics Approval

A total of 5 male and 11 female Beagle dogs (aged, 19-20 months and body weight, 7.0-12 kg) were purchased from Shanghai Jia-Gan Biological Science and Technology Co., Ltd., which was qualified and certified by Shanghai Laboratory Animal Management Committee (SCXK (Hu) 2015-0005). All procedures used in this study were in accordance with our institutional guidelines, which comply with the Animal Research: Reporting of In Vivo Experiments guidelines and were approved by the Animal Care and Use Committee of Nantong University, Nantong, China (no: S20210302-010).

Beagle dogs were kept in kennels at the Experimental Animal Center of Nantong University. The dogs were fed under natural light/dark cycles at a temperature of 16-26°C and 40%-70% relative humidity with free access to tap water. Standard canine food was provided every morning.

Anesthetics Application

The magnetic resonance imaging (MRI) scans were performed under general anesthesia with sodium pentobarbital (Yiji Pharmacy,

Guangzhou, China) (3%) by intramuscular injection at a dosage of 1.3 mL/kg body weight. The experimental dogs were fasted for 10-12 hours before anesthesia, but they were given drinking water ad libitum. Atropine sulfate (King York Pharmacy, Tianjin, China) (0.045 mg/kg) was used 15-20 minutes before anesthesia to decrease the vagus nerve reflex and the secretion of respiratory glands. All Beagle dogs were imaged on a 3.0 Tesla MR scanner (Magnetom VerioM, Siemens Healthcare, Erlangen, Germany) with 8-channel head coil.

Imaging Acquisition

To establish the MRI sequence of the inner ear of the Beagle dogs, we compared the T2-sampling perfection with application-optimized contrasts by using different flip angle evolutions (SPACE), 3-dimensional (D)-fluid attenuated inversion recovery (FLAIR), and 3D-constructive interference steady-state (CISS) sequences and found that the 3D-CISS sequence can simultaneously show the semicircular canals and the cochlea. Therefore, a high-resolution, strongly T2-weighted, 3D-CISS sequence of the temporal bones was performed to evaluate the anatomy of the whole fluid-filled labyrinthine spaces with the following parameters: repetition time (TR) 8.79 ms, Echo time (TE) 4.37 ms, Flip angle (FA) 47°, Field of view (FOV) 140 × 140 mm², 88 slices, base resolution 320, averages 3, slice thickness 0.2 mm, receiver bandwidth 422 Hz/pixel, and acquisition time 29.41 minutes.

Image Processing

Data processing was done using ImageJ Fiji. Figure 1 provides a schematic overview of image processing flow. A region of interest around the inner ear was cropped via a square bounding box on the full head CISS MRI images. We intercepted and enlarged the target area. Using ImageJ Fiji, 3-dimensional reconstruction and volume measurement of the required target area were performed. First, we converted the image to 8-bit (Image-Type-8-bit), carried out scale correction, X, Y, Z axis scale correction, and converted pixels to millimeter. After that, we separately selected the area to be analyzed (Image—Duplicate). We selected the 3D view plugin to reconstruct the 3D view (Plugins—3D Viewer). We could observe the approximate shape of the target in the view by adjusting the threshold. To show the outline of the inner ear, we first selected the “Straight Line” tool as a free curve. Then, we selected the unnecessary areas on the 3D view, right-click, and “Fill selection” from the options to fill the unnecessary areas. After the rough shape appears, we used the “Color Picker” to select the background color in the stock image and the “Brush Tool” to paint, leaving only the target areas. Finally, we used the “3D Object Counter” in “analyze” to calculate the volume (Analyze—3D Object Counter).

Identification of Motion Sickness Susceptibility of Dogs

A rotatory stimulator was used as described in our previous study^{16,17} with reference to the report of Crampton and Lucot.¹⁸ To induce motion sickness, Beagle dogs in the stimulator were rotated in an alternate acceleration and deceleration mode. The acceleration rate was 16°/s² for duration of 7.5 seconds, and a maximal velocity of 120°/s was reached. A duration of 2.5 seconds was used for deceleration with a rate of 48°/s². Clockwise and counter-clockwise rotations were alternately repeated for 60 minutes. The same rotatory test was repeated 2 weeks later. Time to vomit was measured as vomiting latency. An average was calculated from results of two times.

MAIN POINTS

- Magnetic resonance imaging evaluates the inner ear lymphatic fluid volume of Beagle dogs. Motion sickness susceptibility showed a positive correlation with lymphatic volume. The difference in lymphatic volume in the vestibule and cochlea between bilateral inner ears in the insensitive group is greater than that of sensitive group.

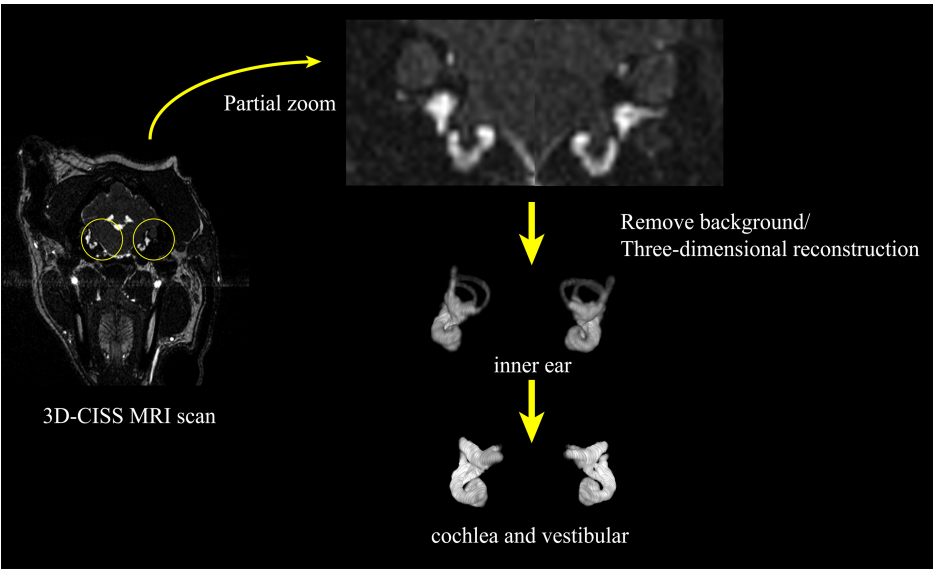


Figure 1. Image processing flow. After the inner ear MRI of the Beagle dogs, we zoomed in, intercepted the inner ear area, and processed the captured image through ImageJ Fiji. First, we corrected the scale, removed the irrelevant background, and finally performed 3D reconstruction. MRI, magnetic resonance imaging; 3D, 3-dimensional.

Statistical Analysis

Statistical analysis was carried out with the IBM SPSS Statistics v.20 software package (IBM SPSS Corp.; Armonk, NY, USA). The Student's *t*-test was used to compare 2 groups of values after the normality test, and the Pearson correlation coefficient was used to evaluate the correlation between 2 parameters. Differences were considered statistically significant at a level of *P* < .05.

RESULTS

Determination of the Susceptibility to Motion Sickness in Dogs

Vomiting was used as an index of motion sickness in dogs. Dogs with vomiting latency of less than 15 minutes were considered sensitive to motion sickness, whereas those with vomiting latency of more than 25 minutes were considered insensitive (Table 1).

According to the above rules, 8 out of 16 Beagle dogs (3 males and 5 females) were selected as motion sickness-sensitive dogs and the other 8 (2 males and 6 females) were motion sickness-insensitive ones with the mean value of vomiting latency in dogs of insensitive group (43.20 ± 11.00) significantly longer than that of sensitive group (8.65 ± 2.41 , *P* < .01, Table 1).

Fluid Volume Analysis of the Inner Ears

Since the inner ears of the Beagle dogs are relatively small, the definition of the semicircular canals was not very high. As a result, we did not obtain clear imaging of the semicircular canal. Therefore, we removed the semicircular canals from the 3-dimensionally reconstructed inner ears, leaving only the vestibule and cochlea for volume analysis (Figure 2).

After a 3-dimensional reconstruction, we performed an analysis of the cochlear and vestibular lymphatic volume of the inner ears.

Table 1. Vomiting Latency of Dogs During Rotatory Stimulation

No.	Sex	Vomiting Latency in Sensitive Group (Minutes)	No.	Sex	Vomiting Latency in Insensitive Group (minutes)
8314	Male	10.70	8301	Male	26.18
8320	Female	5.82	8311	Male	35.48
8322	Male	11.19	8325	Female	40.37
8340	Male	11.03	8327	Female	35.68
8341	Female	5.40	8343	Female	54.18
8357	Female	7.98	8344	Female	45.43
8358	Female	6.91	8366	Female	48.28
8392	Female	10.13	8376	Female	60.00
Mean ± SD		8.65 ± 2.41	Mean ± SD		43.20 ± 11.00*

**P* = .0000005249, vs. sensitive group.
SD, standard deviation.

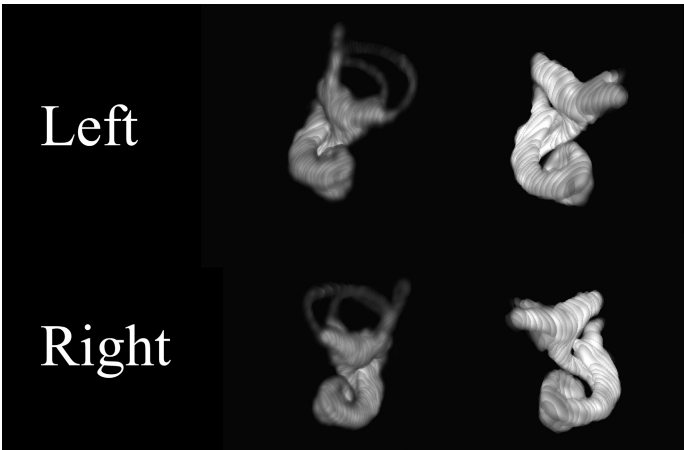


Figure 2. Removal of the semicircular canals on the basis of original 3D reconstruction. (A). Completion of 3D reconstruction of the left ear. (B). 3D reconstruction of left ear with semicircular canal removed. (C). Completion of 3D reconstruction of the right ear. (D). 3D reconstruction of right ear with semicircular canal removed. 3D, 3-dimensional.

Table 2. Lymphatic Volume of the Inner Ears in Sensitive Group

No.	Left Ear (mm ³)	Right Ear (mm ³)	Volume Difference Between Bilateral Inner Ears (mm ³)	Total Volume of Both Ears (mm ³)
8314	56.04	56.69	0.65	112.73
8320	57.74	57.06	0.67	114.80
8322	51.21	49.40	1.81	100.61
8340	56.05	55.92	0.13	111.96
8341	62.23	60.32	1.92	122.55
8357	59.43	59.66	0.24	119.09
8358	59.39	57.43	1.96	116.82
8392	53.48	54.80	1.33	108.28
Mean \pm SD	56.94 \pm 3.53	56.41 \pm 3.37	1.09 \pm 0.76	113.35 \pm 6.78

SD, standard deviation.

The volume of lymphatic fluid in the inner ears of Beagle dogs ranged from 41.69 to 69.09 mm³ (Tables 2, 3). The volume of left inner ear in sensitive group was 56.94 \pm 3.53 mm³, right inner ear was 56.41 \pm 3.37 mm³, and the bilateral volume difference was 1.09 \pm 0.76 mm³ (Table 2). The volume of left inner ear in insensitive group was 55.23 \pm 6.37 mm³, right inner ear was 51.70 \pm 9.32 mm³, and the bilateral volume difference was 5.10 \pm 1.96 mm³ (Table 3).

Though the total lymphatic volume of bilateral inner ears in sensitive group dogs (113.35 \pm 6.78 mm³) was higher than that in insensitive group dogs (106.93 \pm 15.35 mm³), there was no significant difference between 2 groups with different susceptibilities to motion sickness ($P > .05$, Figure 3A). However, the volume difference between bilateral inner ears of dogs in insensitive group was greater than that of dogs in sensitive group ($P < .05$, Figure 3B) with the value in sensitive Beagle dogs all less than 2 mm³ (Table 2).

Correlation of Lymphatic Volume Difference between the Bilateral Inner Ears and Vomiting Latency

Next, we analyzed whether the susceptibility of motion sickness is related to the total lymphatic volume of 2 inner ears or the difference in lymphatic volume between bilateral inner ears. As a result, the Pearson correlation coefficient analysis revealed a weak negative correlativity ($r = -0.2300$, $P > .05$) between the total lymphatic volume of 2 inner ears and the vomiting latency, and it is also insignificant (Figure 3C). Moreover, we found that the difference in lymphatic

volume between bilateral inner ears of Beagle dogs was positively correlated with the latency of vomiting ($r = 0.7544$, $P < .05$), that is, the longer the vomiting latency in the Beagle dogs, the greater the difference of the lymphatic volume between bilateral inner ears (Figure 3D).

DISCUSSION

Although the etiology of motion sickness has been widely explained, there is still no consensus on the detailed mechanism in the development of motion sickness. Meanwhile, the reasons for difference in the susceptibility to motion sickness are still poorly understood. The clinical manifestations of motion sickness are similar to Meniere's disease so we take Meniere's disease as a reference subject. Meniere's disease is caused by endolymphatic hydrop following some structural enlargement.^{13-15,19-20} Therefore, we speculated that the development of motion sickness may be related to changes in the inner ear lymphatic volume.

The lymphatic fluid is present in the labyrinth, making it difficult to quantify. In order to verify whether the development of motion sickness is related to the lymphatic volume of the inner ear, we quantified it using MRI technique. At present, the 3-dimensional reconstruction and volume calculation of the various components of the inner ear is done mainly through computer deep learning.²⁰ An alternative method is that the researchers use the workstation to perform 3-dimensional reconstruction and volume calculation.²¹ The time cost of these methods is relatively high and not conducive to

Table 3. Lymphatic Volume of the Inner Ears in Insensitive Group

No.	Left Ear (mm ³)	Right Ear (mm ³)	Volume Difference Between Bilateral Inner Ears (mm ³)	Total Volume of Both Ears (mm ³)
8301	49.52	45.17	4.36	94.69
8311	49.86	41.69	8.17	91.55
8325	53.59	48.18	5.41	101.77
8327	69.09	67.37	1.72	136.46
8343	58.44	64.72	6.28	123.16
8344	56.43	50.94	5.48	107.37
8366	52.03	46.02	6.01	98.04
8376	52.87	49.50	3.38	102.37
Mean \pm SD	55.23 \pm 6.37	51.70 \pm 9.32	5.10 \pm 1.96	106.93 \pm 15.35

SD, standard deviation.

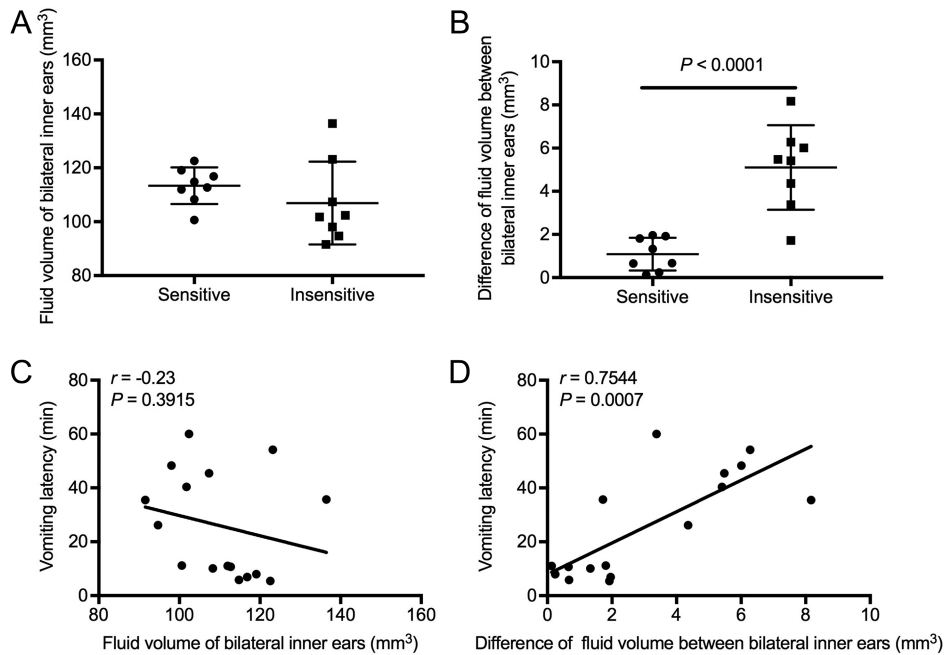


Figure 3. Vestibular and cochlear lymphatic volume in the inner ear of Beagle dogs with different susceptibilities to motion sickness. (A). The total lymphatic volume of vestibular and cochlear compartments in the inner ear of dogs with different susceptibilities to motion sickness ($n=8$ for sensitive group and $n=8$ for insensitive group). (B). The difference in vestibular and cochlear lymphatic volume between bilateral inner ears of dogs with different susceptibilities to motion sickness ($n=8$). (C). Correlation between the total lymphatic volume of vestibular and cochlear compartments in bilateral inner ears and the vomiting latency of dogs. (D). Correlation difference of lymphatic volume between the bilateral inner ears and the vomiting latency of dogs.

clinical application. Through the software ImageJ Fiji, we could quickly observe whether the inner ear is intact by adjusting the threshold. We segmented the image manually to perform 3D reconstruction, which is more effective than machine segmentation. Because the image processing speed is faster, it is more suitable for rapid clinical evaluation of the endolymph.

According to the classical hypothesis of motion sickness, when the human body moves passively, and the received signal upload does not match the velocity store, it will cause motion sickness.^{1,2,22} In a study investigating delayed endolymphatic hydropatients, they found that in the lateral semicircular canal, a functional deterioration could be detected more frequently than morphological changes.²³ Moreover, vestibular-evoked myogenic potentials could detect the signal acceptance difference from 2 sides of the utricle and saccule of different motion sickness susceptibility groups, which may be attributed to inner ear otolith asymmetry.^{8,24} Endolymph hydrops can be found mainly in the vestibule and cochlea as shown by MRI in Meniere's disease.²⁵⁻²⁸ Accordingly, we put forward 2 possibilities with regard to motion sickness: (1) higher volume in lymphatic fluid of the inner ears (particularly the cochlear and vestibular compartments) will elevate the sensitivity of the vestibular receptors to vestibular stimulus and (2) a higher asymmetry of the lymphatic volume between bilateral inner ears will reinforce the sensory conflict. Thereby, the individual susceptibility to motion sickness is supposed to relate to the total volume or an asymmetrical distribution of lymphatic fluid of two inner ears.

In the present study, we first analyzed the inner ear as a whole and found that the total lymphatic volume of 2 inner ears (vestibule plus cochlea) in sensitive group dogs was higher than that in insensitive group dogs, but the difference between 2 groups is not significant

statistically. Meanwhile, the Pearson correlation coefficient analysis revealed a weak negative correlativity ($r = -0.2300$) between the total lymphatic volume of 2 inner ears and the vomiting latency, and it is also insignificant. Because the sample size in this study is small ($n=16$), an exact relationship between the total lymphatic volume of 2 inner ears and the motion sickness susceptibility needs further study in the future by increasing the number of animals.

Secondly, we observed the distribution of lymphatic fluid in 2 inner ears and found that in Beagle dogs with different susceptibilities of motion sickness, lymphatic volume between 2 sides of the inner ear (vestibule plus cochlea) was different, that is, the volume difference between bilateral inner ears in insensitive dogs was greater than that of sensitive dogs. Furthermore, we evaluated the correlation of the lymphatic volume difference between bilateral inner ears with the vomiting latency and found that the difference in lymphatic volume between bilateral inner ears of Beagle dogs was positively correlated with the vomiting latency, that is, the greater the difference of the lymphatic volume, the longer the vomiting latency. This result means that Beagle dogs with bigger volume difference of lymphatic fluid between 2 sides of the inner ear will have longer vomiting latency, that is, lower susceptibility to motion sickness and being more resistant to motion sickness. Present results suggested a bigger asymmetrical distribution of lymphatic fluid of 2 inner ears in the basic state of Beagle dogs that are insensitive to motion sickness.

Vestibular asymmetries between 2 sides of the inner ear are also reported by other researchers, including asymmetries of otoliths (utricle or saccule or both otoliths)^{8,29-31} and semicircular canals,³² especially in elicited vestibular responses after vestibular stimulations including caloric stimulus, rotatory stimulus, and changed gravity stimulus^{24,33-36} or optokinetic stimulus.³⁷ However, the symmetry of

lymphatic fluid distribution in bilateral inner ears is not well known at present. Kendi et al³⁸ assessed right and left inner ear fluid volumes in 29 human subjects (13 males and 16 females) and found that left semicircular canal/vestibule volume of female subjects was higher than that of male subjects and that difference between right and left semicircular canal/vestibule volumes of female subjects was higher than that of male subjects. Nevertheless, they do not know the relationship between lymphatic fluid distribution in the inner ears with motion sickness susceptibility. The present study is the first report on the relationship between asymmetric distribution of lymphatic fluid in bilateral inner ears with motion sickness susceptibility. Similarly, Kuldavletova et al³⁹ recently also reported a significant asymmetry in otolith-driven ocular response in pilots that were less susceptible to motion sickness as compared to normal volunteers.

However, why do the subjects with lower susceptibility to motion sickness present higher asymmetry in the distribution of lymphatic fluid in bilateral inner ears we found in dogs in this study or higher asymmetry in the otolith-driven ocular response Kuldavletova et al³⁹ reported in pilots? In general, the inner ears with a higher asymmetry of the lymphatic volume between bilateral inner ears will transmit conflict signals to the central nervous system and reinforce the sensory conflict, which will be easy to cause motion sickness according to the theory of sensory conflict. It is similar to the usual observation that patients with unilateral vestibular loss in the acute phase may be more sensitive to motion.¹⁰ However, many researchers consider that interaural otolith asymmetry would be centrally compensated under terrestrial conditions, but on exposure to weightlessness, the persisting central compensation would produce a central imbalance that could lead to motion sickness.^{36,40-42} Moreover, the patients with unilateral vestibular loss also have decreased susceptibility to motion sickness after the acute phase, but to a lesser extent than bilateral vestibular loss, here, it should be noted that these were “compensated” patients who have adapted to sensory conflict caused by the loss of vestibular function on one side.¹⁰ In the same way, we consider that due to the bigger volume difference between 2 sides of the inner ear lymphatic fluid in the insensitive group, the Beagle dogs have been in a state of moderate adaptive compensation potentially through central regulation in the brain, which makes the animals more resistant to the vestibular stimulation. In contrast, in the sensitive group, due to the smaller difference in the lymphatic volume of 2 side inner ears, the animals have weak central regulation ability, which makes them less resistant to an abnormal vestibular stimulation.

Because the lymph of the inner ear is connected between the cochlear and the vestibular parts, any changes in lymph volume are almost accompanied by the changes in pressure, may also with the changes in viscosity or osmotic pressure, and as a result, will exert influences on the fluid dynamics of the endolymph. Thereby, the mechanosensitivity of the hair cells in cochlea and vestibule will be affected. In addition to hearing, it will change the effect of vestibular stimulation on the inner ear. Therefore, asymmetric distribution of the lymphatic fluid volume in the bilateral inner ears will affect the vestibular function and also the occurrence of motion sickness, including motion sickness susceptibility.

The present study suggests a relationship between the difference in lymphatic volume of the bilateral inner ears and the

susceptibility of Beagle dogs to motion sickness. Vestibular autonomous response is usually caused by abnormal changes in endolymph. However, we do not know the endolymphatic volume of the bilateral inner ear under basal status of normal subjects at present, especially the changes during vestibular stimulation, which is an interesting subject worthy of new study. Moreover, the underlying molecular mechanism is also needed to investigate through further experiments.

CONCLUSIONS

Magnetic resonance imaging could be used as a method to evaluate the inner ear lymphatic fluid volume of Beagle dogs with different susceptibility to motion sickness, through which we found that motion sickness susceptibility is related to the difference in lymphatic volume in the vestibule and cochlea between bilateral inner ears, and the larger the volume difference, the lower the sensitivity.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Nantong University (approval no: S20210302-010).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception – Z.J.; Design – M.C., L.C., X.Z., Z.J.; Supervision – L.C., J.X., L.X., X.Z., Z.J.; Funding – X.Z., Z.J.; Materials – M.C., L.X.; Data Collection and/or Processing – M.C., J.X., L.X., C.R.; Analysis and/or Interpretation – M.C., L.C., J.X., L.X., C.R., X.Z.; Literature Review – M.C., L.C., J.X., L.X., C.R., X.Z., Z.J.; Writing – M.C., L.C., X.Z., Z.J.; Critical Review – M.C., X.Z., Z.J.

Declaration of Interests: The authors have no conflict of interest to declare.

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