Inner Ear Pressure Evaluation using Wideband Tympanometry in Children with Large Vestibular Aqueduct Syndrome (LVAS): A pilot study

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Abstract

Objective: To investigate middle ear function in children with Large Vestibular Aqueduct Syndrome (LVAS) to explore the feasibility of measuring inner ear pressure using Wideband tympanometry (WBT).

Methods: 13 children with LVAS, aged from 3 to 11 years old, were recruited. WBT and other audiological measurements i.e., Auditory Steady State Response (ASSR), Auditory Brain Stem Response (ABR), and Distorted Product Otoacoustic Emissions (DPOAE) were performed. Absorbance under ambient and peak pressure were compared with normative data, and analyzed using a one sample t-test.

Results: Average absorbance in children with LVAS was significantly lower than normative data under ambient pressure at 1000, 1189, 1296, 2000 Hz and 4000 Hz. Absorbance under peak pressure was also significantly lower at 707, 794, 917, 1000, 1189, 1297, 1498 and 2000 Hz. However, absorbance was higher than standard values above 4000 Hz under ambient and peak pressure. It was also higher under ambient pressure at frequencies below 500 Hz.

Conclusion: The special characteristics of middle ear function found in children with Large Vestibular Aqueduct Syndrome (LVAS) indicate that WBT offers a sensitive and non-invasive method to evaluate inner ear pressure indirectly.

Abbreviations

LVAS	Large Vestibular Aqueduct Syndrome
WBT	Wideband tympanometry
EVA	Enlarged Vestibular Aqueduct
SAC	Static Acoustic Compliance
RF	Resonant Frequency
CT	Computed Tomography

1. Introduction

Large Vestibular Aqueduct Syndrome (LVAS) was first reported as a Ménière's-like disturbance by Clemis in 1967 [1]. Advances in radiological techniques enabled Valvassori and Clemis [2] to observe that 50 patients in a group of 3700 consecutive patients referred for tomography of inner ear structure, had abnormally enlarged vestibular aqueducts, with diameters greater than 1.5 mm, and consequently re-named this group of patients as LVAS. The etiology of LVAS is mainly due to dysplasia of the endolymphatic duct at the embryonic stage and mutations of genes such as SLC26A4. From radiological evidence, an enlarged vestibular aqueduct may be accompanied by other inner ear malformations, such as hypoplasia, incomplete partition and anomalies of the semicircular canals and vestibule [3].

It has been generally accepted that children with LVAS typically show progressive, high-frequency and usually bilateral sensorineural hearing loss (SNHL) at an early age. Some might also have other symptoms for example vertigo. Furthermore children with LVAS are more prone to suffer sudden hearing loss with small intracranial pressure changes caused by head trauma, crying or the Valsalva maneuver [4,5].

There has been some speculation as to the mechanisms that cause sensorineural hearing loss in children with LVAS, especially after head trauma, however they are still not clearly understood. Gussen [6] examined temporal bone specimens that had bilateral Mondini malformations with bilateral widened vestibular aqueducts. Severe bone erosion of the vestibular aqueduct was found, suggesting that pressure within the endolymphatic duct and sac caused erosion of the surrounding bone. Such evidence indicates a relationship between bone erosion and chronically increased inner ear pressure in patients with an enlarged vestibular aqueduct (EVA). In addition, Jackler et al. [7] proposed that a dysfunctional sac would affect electrolyte balance in the inner ear and disturb the homeostasis of the internal inner ear environment, which would damage the function of hair cells and consequently lead to hearing loss.

It is generally accepted that abnormal transmission of cerebrospinal fluid (CSF) pressure is the main reason for pressure fluctuations and subsequent pressure increases in the inner ear through the EVA [7]. Previous studies have shown that change in CSF pressure was associated with pressure change in perilymphatic [8], with no significant difference between the perilymphatic and endolymphatic pressure. Therefore a correlation between CSF pressure and the pressure in the inner ear has been proposed [9–12].

According to Takeuchi et al. [10,12], infusion of saline through the subarachnoid caused an increase of pressure in the perilymph and a simultaneous increase of the pressure in the endolymph, suggesting that cerebrospinal fluid pressure is transmitted to the endolymph through the perilymph. Pressure changes within the labyrinth may affect microvascular blood flow or micromechanical systems in the inner ear [13]. An increase in lymphatic pressure in the inner ear can compress blood vessels, which can affect blood flow and ultimately affect the function of hair cells. Therefore, the mechanism proposed underlying sudden hearing loss caused by trauma or crying is that a sudden increase in cerebrospinal fluid pressure can be transmitted to the endolymph, which could disrupt the internal environment, blood flow and lead to damage of the hair cells.

To verify the hypothesis that increased inner ear pressure causes reduced compliance at the tympanic membrane (TM) and influences TM displacement, recent studies have utilized measurements of static acoustic compliance (SAC) [14–16], tympanic membrane displacement (TMD) [17–19] and resonant frequency (RF) [20,21].

The studies by Hall et al. [15] and Levent et al. [16] showed that low static acoustic compliance could be easily observed in patients with Ménière’s disease (MD). Yazawa et al. [22] found endolymphatic hydrops in 93% MD patients suggesting an increased inner ear pressure in MD patients. However, a 30% incidence of low static compliance had been observed on normal people and 60% in patients with Ménière’s disease in the study of Levent et al. [16], which shows the sensitivity and specificity of the static acoustic compliance to be low. Other studies revealed that tympanic membrane movement was affected by inner ear pressure when it was measured using either microflow [17] or laser Doppler interferometry [18] on human temporal bones. Although both methods demonstrate the effect of inner ear pressure on the tympanic membrane vibration, they are often used only for research purposes because of the complex instrumentation and methodologies required.

Multifrequency tympanometry has been used to detect RF in patients with inner ear disorders. Franco-Vidal et al. [20] found decreased RF in patients with MD using a Grason Stadler GSI 33 (Version 2), indicating an association between inner ear pressure and RF. They concluded that multifrequency admittancemetry could be useful in the management of not just MD as decreased RF has also been observed in LVAS [23,24]. However, poor sensitivity and specificity of RF (41.3% and 84.2%, respectively) were found in the detection of Ménière’s disease according to the report of Sugasawa et al. [21]. In addition, diverse RF results were found in LVAS patients under different hearing situations [25]. Bilgen et al. [25] suggested that this might be related to a different mechanism of LVAS. “The third window”, i.e., cochlear aqueduct and enlarged vestibular aqueduct, releases cochlear pressure to decrease inner ear impedance [24] and the increased inner ear pressure in LVAS leads to increased acoustic impedance [25].

Therefore, multifrequency tympanometry appears to be an effective tool to explore the influence of inner ear pressure on the middle ear sound transmission mechanism. However, there are limitations in evaluating inner ear pressure when RF is used in clinical practice.

Wideband absorbance tympanometry (WBT) is a newly commercialized middle ear analyzer, providing an effective tool to measure dynamic middle ear function in the frequency range 250 to 8000 Hz. Compared with traditional tympanometry, not only has it a wider testing frequency range, but it can also provide more detailed information, such as resonant frequency and dynamic characteristics of the middle ear. Several recent studies have demonstrated its effectiveness in the diagnosis of some middle ear disorders, especially in the identification of conductive hearing loss disorders (CHL), such as secretory otitis media (SOM) [26], otosclerosis [27] and ossicular chain disruption [28]. For example, Keefe et al. [29] compared the test performance of WBT absorbance and 226 Hz tympanometry in detecting conductive hearing loss, and found that the likelihood-ratio predictors for wideband absorbance at ambient and tympanometric pressure was higher (0.97 to 0.93) than the predictors for 226Hz tympanometry (0.80 to 0.93) in terms of the accuracy of the test. In addition, Shahnaz et al. [27] showed that 82% of otosclerotic ears were identified with a low false positive rate. These data suggest that WBT is a highly sensitive measure of mild changes to middle ear status [27,29,30].

Considering the relationship between inner ear pressure change and the possible corresponding changes in the middle ear compliance, together with the advantages of the WBT, this pilot study set out to investigate the characteristics of WBT in children with LVAS in order to explore the feasibility of measuring inner ear pressure using the WBT.

2. Materials and Methods

2.1 Participants

A total of 24 ears were tested from 13 children (7 boys and 6 girls) with LVAS, aged from 3 to 11 years old. They were recruited between May 2018 and January 2019 in the Department of Otolaryngology Head and Neck Surgery, Beijing Tongren Hospital, Capital Medical University, China.

Patients were diagnosed as LVAS by computed tomography (CT), when VA diameters (vertical and axial width on the midpoint between labyrinth and operculum) were greater than 1.5 mm.

Inclusion and exclusion criteria were as follows.

(1) No history of other acquired ear diseases (such as otitis media);

(2) No acute or chronic upper respiratory inflammation;

(3) Normal 226Hz tympanometry with type-A peak, peak pressure within the range -100 and +50 daPa;

(4) Normal TM and Eustachian tube at the time of participation.

(5) Considering the fact that the changed (negative or positive) pressure would increase the stiffness of the middle ear and the lower frequency damping [31], which may have influence on our results, abnormal peak pressure was excluded.

In compliance with ethical standards for human subjects, written informed consent was obtained from parents or carers on behalf of all participants before proceeding with the study procedures. This study was approved by the Institutional Review Board in Beijing Tongren Hospital, Capital Medical University.

2.2 Procedures

2.2.1 Routine clinical investigations

All participants underwent a routine otorhinolaryngological examination, followed by audiological tests and a CT scan. To investigate audiological status in terms of hearing level and function of the central auditory system, together with the development of the auditory system, several audiological tests were performed, including: 1) Auditory Steady State Response (ASSR) (Intelligent Hearing System), 2) Auditory Brain Stem Response (ABR) (Interacoustics), and 3) Distorted Product Otoacoustic Emissions (DPOAE) (Otodynamics, ILO 92 analyzer), 4) conventional low frequency tympanometry (Grason Stadler Instrument (GSI) TympStar) and 5) WBT (Titan IMP440, Interacoustics).

To explore middle ear function, the 226 Hz tympanogram, acoustic compliance and pressure of tympanic cavity were recorded. In addition, energy absorbance (EA) at ambient pressure, EA at peak pressure and resonance frequency (RF) were also measured using the WBT.

2.2.2 **Measurement of WBT**

A commercial Titan IMP440 middle ear impedance device (Interacoustics, Denmark, Version 3.4) was used to measure the absorbance of the middle ear from 226 to 8000 Hz at a pressure sweep from -300 to +200 daPa at a rate of 100 daPa/s [32]. A Titan standard probe was used to record absorbance using an appropriate measurement protocol. A probe validity check was performed using the 2cc cavity built-in to the Titan cradle. A suitable ear tip was carefully selected to ensure a proper fit and a good seal of the ear canal. WBT measurement was conducted at least 3 times by re-fitting the probe for each measurement in order to obtain reliable results. All participants were managed to remain quiet and still during the entire duration of the measurements.

2.2.3 Normative data used in the present study

The commercial Titan measurement device provides a specific recording protocol as well as the normative range for infants, which is commonly used for comparing and interpreting measured results in ENT/Audiology clinics. In the present study, normative data of the 10th percentile and the 90th percentile absorbance at both ambient pressure and peak pressure for children aged from 3 to 11 years old was obtained from the Interacoustics Company, which appears age and gender appropriate.

2.3 Data analysis and Statistical Tests

The absorbance measured using the commercial Titan device was exported using the Titan research module. All data on age, gender, hearing condition, static acoustic compliance and absorbance were imported and analyzed using SPSS 22.0. A one sample *t*-test was used for statistical analysis. The level of significance was set at the conventional 5% level in each case.

3. Results

- **Demographic information and audiological characteristics of the children that participated in the study**

Table1 summarizes the general information for participants including; demographic data, affected ear side, hearing status and CT results. Out of the 13 children recruited, 12 (12/13, 92.3%) had bilateral LVAS. Only one case (Case 4) showed unilateral LVAS. According to the inclusion and exclusion criteria mentioned in the methods section, the left ear in Cases 13 was excluded due to abnormal tympanometry (Type C tympanogram). As a result, 24 ears (from 13 children) between 3 and 11 years old were included for data collection.

Table 1: Demographic information and audiological characteristics of the children that participated in the study

Case	Age	Gender	Side	Hearing Status	226Hz Tympanometry			WBT	CT
					AI*	SAC (cc)	PP (daPa)	RF (Hz)	Malformation Category
1	6	F	R	Profound	A	0.5	-10	426	LVAS
			L	Profound	A	0.5	-5	485	LVAS
2	9	F	R	Moderate	A	0.3	-15	868	LVAS
			L	Severe	A	0.4	-20	880	LVAS
3	4	M	R	Severe	A	0.4	-15	586	LVAS
			L	Severe	A	0.4	-15	834	LVAS
4	5	F	R	Profound	A	0.45	-78	879	LVAS
5	9	F	R	Severe	A	0.3	-20	607	LVAS
			L	Profound	A	0.3	-40	575	LVAS
6	3	M	R	Profound	A	0.8	-20	858	LVAS
			L	Severe	A	0.6	40	641	LVAS
7	5	F	R	Profound	A	0.6	-5	973	LVAS
			L	Profound	A	0.3	10	1106	LVAS
8	6	M	R	Severe	A	0.57	-18	872	LVAS
			L	Profound	A	0.6	25	693	LVAS
9	3	F	R	Profound	A	0.3	25	521	LVAS
			L	Severe	A	0.3	10	411	LVAS
10	4	M	R	Profound	A	0.4	45	545	LVAS
			L	Profound	A	0.6	40	380	LVAS

11	4	M	R	Severe	A	0.4	-20	343	LVAS
			L	Profound	A	0.5	-5	377	LVAS
12	6	M	R	Severe	A	0.4	-30	635	LVAS
			L	Severe	A	0.2	-5	557	LVAS
13	4	M	R	Severe	A	0.3	20	985	LVAS

**AI: Type of curve in traditional 226 Hz tympanometry.*

- **Characteristics of absorbance at ambient pressure and peak pressure in children with LVAS**

Figures 1 and 2 show absorbance at ambient pressure and peak pressure obtained from children with LVAS in comparison to normative data provided by the Interacoustics Company. The average of the 10th percentile and the 90th percentile of normative data in the same age band were used as a standard value for the statistical analysis. In general, the absorbance in children with LVAS was lower than the standard value of the normative data over the frequency region between 700 and 2000 Hz. However, the absorbance obtained from children with LVAS was higher at high frequencies above 4000 Hz under ambient and peak pressure or under ambient pressure below 500 Hz.

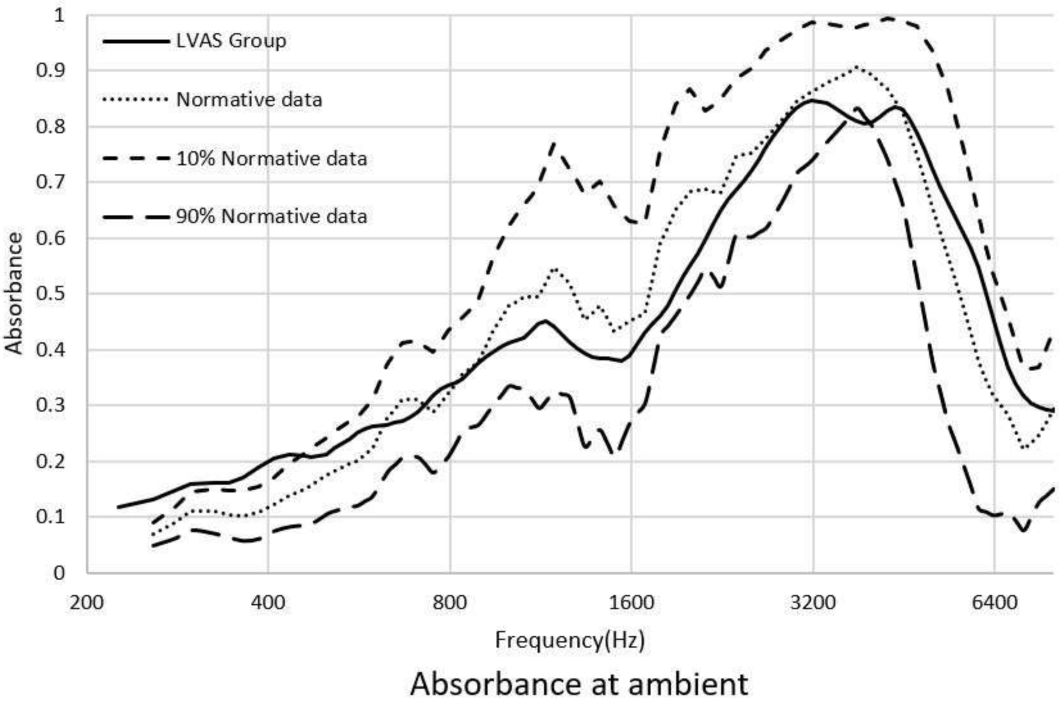

Figure 1. Comparison of absorbance at ambient pressure between LVAS Group and normative data. Normative Data presents the average of the 10th percentile and the 90th percentile.

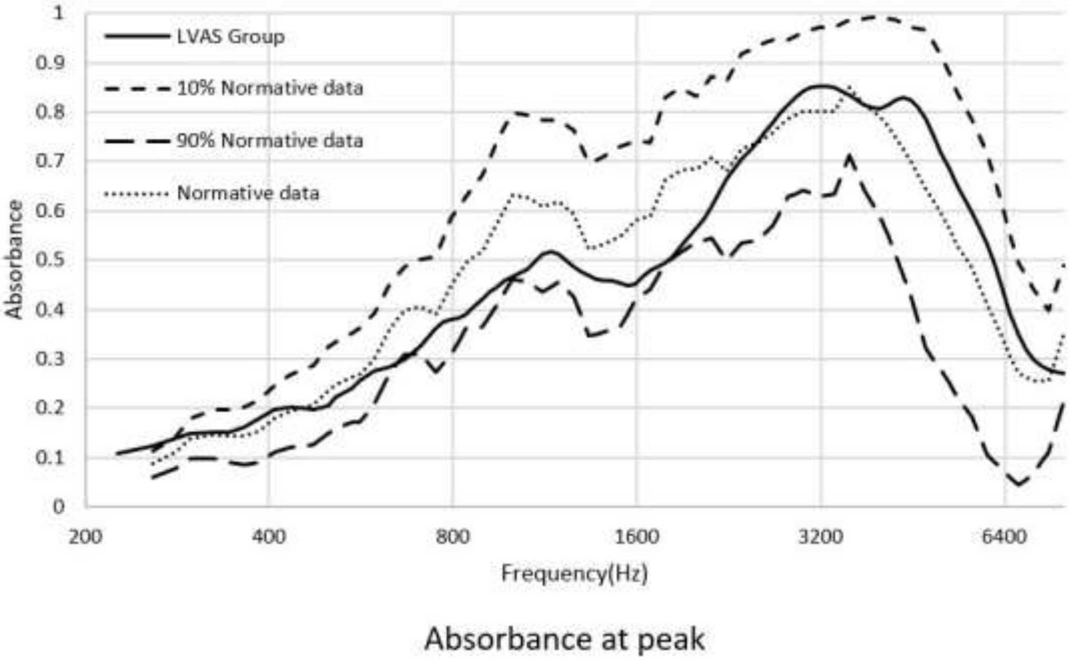

Figure 2. Comparison of absorbance at peak pressure between LVAS Group and normative data. Normative Data presents the average of the 10th percentile and the 90th percentile.

According to the study by Keefe et al. [33], the most effective frequency range to detect middle ear transmission function is between 1 kHz and 4 kHz. Therefore, in the present study, absorbance data at twelve frequencies from 500 Hz to 4000Hz were used in the statistical analysis to verify the differences between children with LVAS and normative data. Table 2 shows the absorbance at different pressures. Results revealed a statistically significant difference at some frequencies. For the absorbance measured at ambient pressure, the absorbance was significantly different at frequencies of 1000, 1189, 1297, 2000, 4000Hz, while the absorbance of the LVAS group measured at peak pressure was significantly lower than the standard values of the normal range at frequencies of 707, 794, 917, 1000, 1189, 1297, 1498, 2000 Hz, but higher at 257, 5040, 5993, 6924 Hz.

Table 2: Characteristics of absorbance at ambient pressure and peak pressure in children with LVAS

Frequency (Hz)	Absorbance at Ambient			Absorbance at Peak		
	LVAS	Normal	*p* –Value	LVAS	Normal	*p* –Value
500	0.2122	0.1744	NS	0.2236	0.2367	NS
595	0.2618	0.2242	NS	0.2924	0.3012	NS
707	0.2884	0.3114	NS	0.3398	0.4065	<0.05
794	0.3355	0.3218	NS	0.3933	0.4475	<0.05
917	0.3870	0.4053	NS	0.4440	0.5463	<0.05
1000	0.4118	0.4778	<0.05	0.4690	0.6312	<0.05
1189	0.4424	0.5469	<0.05	0.5003	0.6196	<0.05

1297	0.4027	0.4874	<0.05	0.4642	0.5587	<0.05
1498	0.3823	0.4326	NS	0.4448	0.5472	<0.05
2000	0.5510	0.6842	<0.05	0.5586	0.6837	<0.05
2997	0.8335	0.8436	NS	0.8262	0.8022	NS
4000	0.8073	0.8922	<0.05	0.8101	0.7912	NS

NS indicates not significant (p>0.05).

- **A special case report:**

Case 4 was a 5-year-old female with a single side LVAS. According to her audiological test and CT results, shown in Figure 3, she was diagnosed as right ear LVAS. She was found to have poor hearing in her right ear during her physical examination at kindergarten. There was no history of middle ear disease and otorhinolaryngological examination showed normal external auditory canals and tympanic membranes bilaterally. Since the right ear peak pressure was 0 daPa, and the left ear peak pressure was -3 daPa, i.e., they were all close to 0 daPa, the curve of absorbance at peak pressure and ambient pressure were basically overlapped. Figure 4a shows that the absorbance of the right ear was 0.04 at 226Hz, and increased with increasing frequency to the first peak of 0.3 near 1100 Hz, and decreased to lower values around 1600 Hz, then increased to the maximum of approximately 1.0 around 4000 Hz. While in Figure 4b, the basic trend of the curve was similar to the right ear, but the first peak is about 0.55 at 1155 Hz, much higher than the right ear. Compared with the absorbance at ambient and peak pressure of her two ears, we can see that the LVAS ear has a lower absorbance from 794 to 2748 Hz, with the biggest difference at 1155 Hz. Figure 4c and 4d are the three-dimension tympanograms of both ears. We can note that below 2 kHz, both ears had a single peak near 0 daPa, but a higher value than the normal ear. They were more complex at high frequency with absorbance peaking near 4000 Hz.

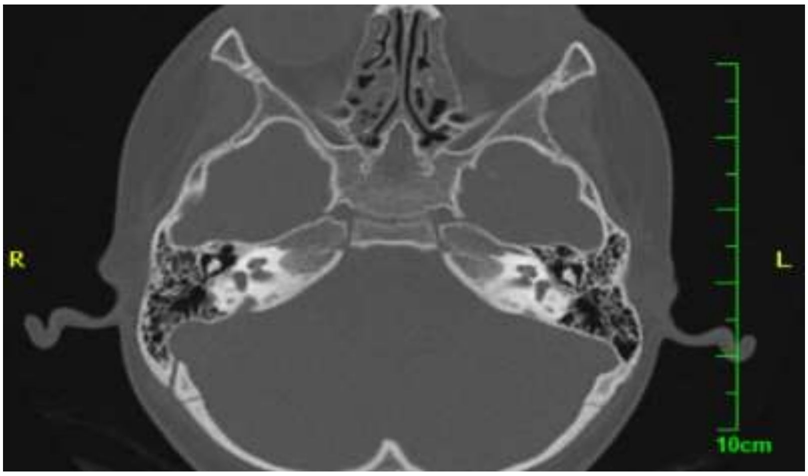

Figure 3. Computed tomography image of Case4. The right ear has an enlarged vestibular aqueduct, while left ear does not.

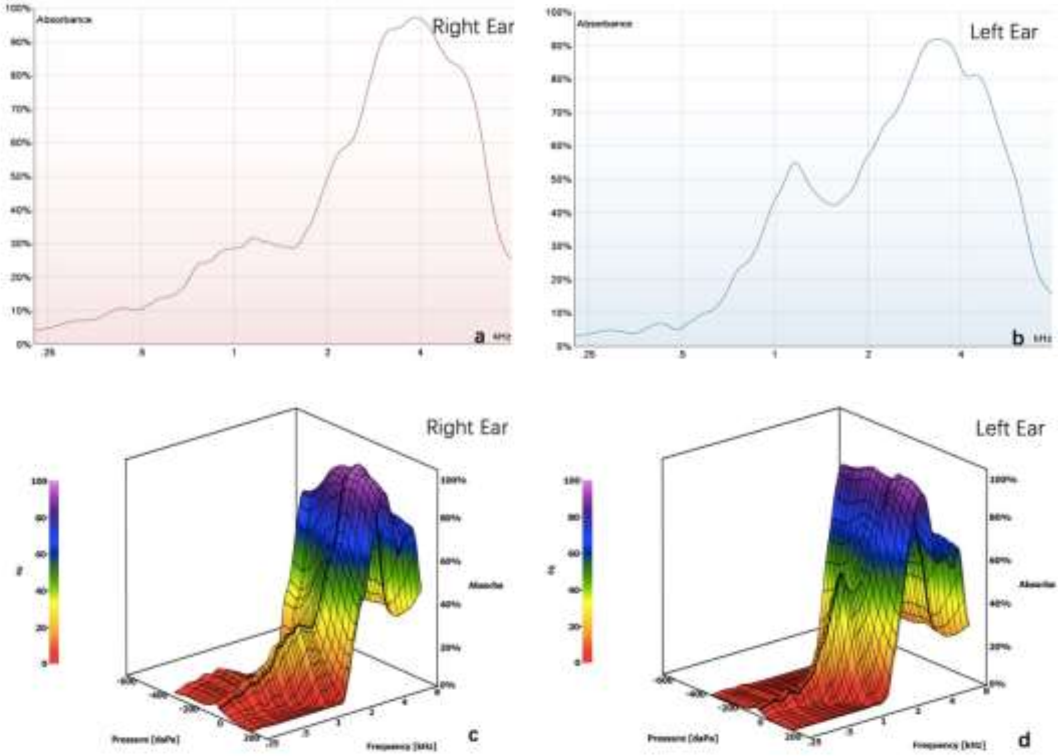

Figure 4. Absorbance and 3D-Tympanometry of Case 4's right ear and left ear at ambient pressure and peak pressure. 4a and 4c are the wideband tympanometry results of right ear with EVA, while 4b and 4d are the results of left ear.

4. Discussion

Indirect clinical evidence has led people to suspect that LVAS patients have increased inner ear pressure. For instance, abnormally high pulsations are often observed on patients with LVAS during cochlear implantation [34]. This phenomenon is explained as the continuous CSF pressure transmission into the cochlea via the enlarged vestibular aqueduct. Such increased intracranial pressure could lead to increased inner ear pressure via the enlarged vestibular aqueduct.

Although several measurements have been proposed to examine inner ear pressure such as inserting a micropipette into the Scala Tympani and Scala Media [9], these invasive measurements are not suitable for clinical use. There are however several indirect methods to measure human inner ear pressure such as; static acoustic compliance [14–16], tympanic displacement [17–19] and resonance frequency [20,21]. However, they either have low sensitivity and specificity in identifying increases in inner ear pressure [16,21], or are too complicated to be widely used in clinical practice.

According to Goode et al. [14], maximum compliance would be expected to decrease particularly at 660 Hz in patients with perilymphatic hypertension. This shows that sensitivity of acoustic compliance is dependent on frequency, hence a single frequency tympanometry, i.e., 226 Hz for adults and 1000 Hz for children, cannot accurately reflect the influence of inner ear pressure change on the middle ear.

Measurement of tympanic membrane displacement is a sensitive way to detect subtle changes of the tympanic membrane. In Myers' study, the amplitude of umbo velocity under increased inner ear pressure, measured by a Laser Doppler Interferometer, decreased below 1000 Hz while increasing at around 2000Hz [18]. This is similar to patients with otosclerosis where there is a lower magnitude of velocity transfer function, especially at frequencies less than or equal to 1,000 Hz [35]. The similarity in results from increased inner pressure and otosclerosis may suggest their mechanisms are similar too. There is usually an abnormal movement of the stapedial footplate in otosclerosis. A fixed stapes causes an increased stiffness of the middle ear and an increased inner ear pressure would also lead to increased stapes-footplate impedance.

However again the specificity of the instrument limits its clinical use, and tympanic membrane displacement measurement is mainly used for scientific research.

Sato [23] and Nakashima [24] observed lower RF in LVAS patients with stable hearing loss compared with normal people. The average resonant frequency of adult LVAS patients was about 778 Hz [23,24]. This is much lower than the average resonant frequency of the normal control subjects which equals 950 Hz approximately.

However, in the study by Bilgen et al. [25], two LVAS patients with fluctuating hearing loss were found to have lower compliance and higher RF (1400 Hz and 1300 Hz) compared with normal individuals. The different results in RF may be related to the different hearing situation of subjects and the different mechanisms [25]. Considering the above information, RF could be an effective indicator for evaluating inner ear pressure, but with a modest diagnostic accuracy.

Because otosclerosis and elevated inner ear pressure have similar TMD results at lower frequency [18,35], they may also have similar WBT results. Under increased impedance, reflected energy would change after sound energy was transferred to the cochlear through the tympanic membrane, ossicular chain, and vestibule window. In the present study significantly lower absorbance data were obtained at frequencies of 1000, 1189, 1297, 1498, 2000 Hz at peak pressure and ambient pressure. According to Shahnaz’s study, 71% of otosclerotic ears had higher reflectance, i.e., lower absorbance, below 1 kHz and 10% of otosclerotic ears exceeded the 90th percentile of normal ears above 1500 Hz [27]. Therefore, the present similar results can also be interpreted to show an increased stiffness of the middle ear caused by increased inner ear pressure. While the frequency related differences may be related to the different ages of the subjects and differences in stiffness between the otosclerosis and increased inner ear pressure situations.

In Figure 5 which compares the absorbance of the LVAS Group under two different pressures, the absorbance at peak pressure is seen to be higher than the absorbance at ambient pressure in the frequency range of 500-1800 Hz. This may be due to the compliance at static pressure. The absorbance at peak pressure is measured with the smallest pressure difference between the inside and outside of the tympanic membrane. In these circumstances, the pressure in the tympanic cavity has little effect on the tympanic membrane activity [32]. In our study, the absorbance data have a significant difference at 707, 793, 917, 1498 Hz under peak pressure, while there is no significant difference at ambient pressure. Therefore, this may provide clinical guidance for the use of absorbance data at peak pressure.

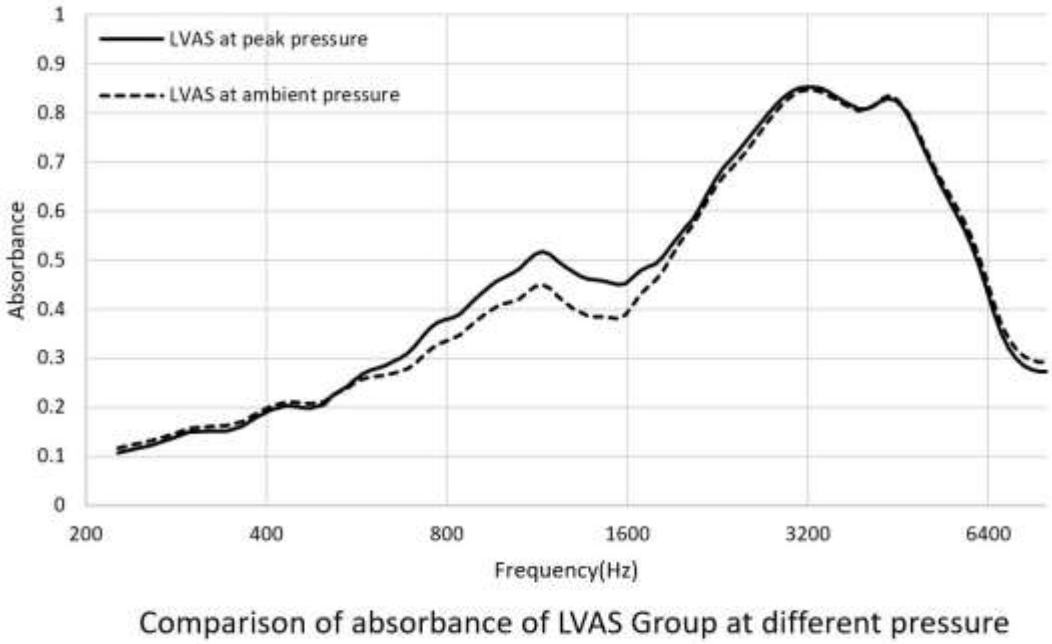

Figure 5. Comparison of average absorbance of LVAS Group at peak pressure and ambient pressure.

It is noteworthy that the absorbance data obtained from children with LVAS increased below 500 Hz and above 4000 Hz. In clinics, such phenomena are quite commonly seen in some patients with middle ear disorders, i.e., absorbance values at several frequencies higher than the normal data. Several clinical and theoretical studies suggest that it may be related to the resonance of middle ear cavity, the standing-wave, and the air-leak [36,37]. For example, Motallebzadeh et al. [36] used the fluid-structure finite-element model to measure the wideband acoustic input admittance, and found the two peaks at 5.0 kHz and 6.4 kHz are related to the resonance of the middle-ear cavity and standing-wave. Therefore, the resonance of the middle ear cavity and standing waves may influence absorbance measurement at the high frequencies.

The increased absorbance at low frequencies found at ambient pressure in the present study unfortunately remains unexplained. The study by Groon et al.[37] revealed that the air leakage led to an increase in the absorbance at the low frequencies (<500 Hz). Therefore, the increased absorbance at the low frequency may be related to an undetectable air leak in the process of testing because of fast the pressure changes from -300 to +200 daPa during the test.

The present pilot study needs to be considered in light of its limitations. Because LVAS is a rare disease in children, the sample size of this pilot study is relatively small. The other limitation is that normative data used in the present study was provided from the Interacoustics company. Although it is reasonable approach and appears age appropriate, there might be a certain level of bias due to demographic differences [38]. Therefore, the present results need to be read with caution. A further study with appropriate sample size to enable comparison of children with LVAS and age- and gender-matched controls is needed in order to provide more reliable evidence of possibility for assessing the increased inner ear pressure by WBT in children with LVAS.

5. Conclusion

Significantly lower absorbance at 700-2000 Hz was found in children with LVAS aged from 3 to 11 years. It indicates that WBT appears a sensitive and non-invasive method to evaluate inner ear pressure indirectly, and thus provides a useful diagnostic tool for assessing patients with LVAS. Future studies should be conducted to investigate the characteristics of the absorbance using the WBT in a large sample size across different age groups in order to verify the findings derived from this pilot study. Furthermore, if it is the case, it would be useful to investigate the correlation between the absorbance and degree of hearing loss in patients with LVAS.

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