



# Wideband Acoustic Absorbance in Otosclerosis: Does Stapedotomy Restore Normal Tympanic Cavity Function?\*

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## Abstract

**Introduction** Otosclerosis is characterized by the fixation of the stapes to the oval window, thereby impairing acoustic signal absorbance. A commonly used surgical technique for improving hearing in cases of otosclerosis is stapedotomy. However, it is unclear whether this surgery restores all the physical characteristics of the tympano-ossicular system.

**Objective** To evaluate the tympano-ossicular system in individuals with fenestral otosclerosis pre and poststapedotomy using wideband tympanometry.

**Method** A total of 47 individuals and 71 ears were assessed. The subjects were divided into three groups: presurgery otosclerosis; postsurgery; and a control group of normal-hearing adults. A handheld tympanometer with a wideband module (226–8,000 Hz) was used to take measurements at ambient pressure and under pressurized conditions. The level of statistical significance adopted was  $p \leq 0.05$ .

**Results** Acoustic absorbance at 226 Hz was low for all groups. At frequencies in the range 630 to 5,040 Hz, each group had a characteristic absorbance curve, allowing them to be distinguished from one another. In the presurgery group, absorbance values were below normal levels, with energy absorbance below 10%. Low energy absorbance was most evident at 1,000 Hz in the presurgery group, but this was not observed in the postsurgery group. Although there was an improvement in hearing, the surgery failed to restore the tympano-ossicular system to normal.

**Conclusion** Wideband acoustic absorbance proved able to differentiate normal ears and otosclerotic ears pre and postsurgery, under both ambient pressure and pressurized conditions.

## Keywords

- ▶ middle ear
- ▶ acoustic impedance tests
- ▶ otosclerosis

\* Work developed at Irmandade da Santa Casa de Misericórdia de São Paulo, São Paulo/SP, Brazil.

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## Introduction

Fenestral otosclerosis, the most common form of the condition, is characterized by abnormal bone growth in the inner ear, which causes the stapes to stiffen and become immobile, thus impairing acoustic signal absorbance (particularly for low frequency sounds) and sound transmission through the tympano-ossicular system to the cochlea.<sup>1</sup> Stapedotomy is one of the main surgical procedures performed in the middle ear, and it seeks to restore hearing in individuals with the condition. The procedure involves the insertion of a prosthesis in the middle ear, affecting its mechanical and acoustic properties while changing its impedance.<sup>2,3</sup>

The audiological techniques for the diagnosis and assessment of otosclerosis are based on the premise that otosclerosis typically increases the stiffness of the middle-ear system, translating to changes in high impedance.<sup>4</sup> The most effective measures for diagnosing otosclerosis are those which assess the relative contributions of mass, stiffness, and resistance. However, there is significant overlap between healthy and otosclerotic ears in measurements obtained using conventional tympanometry with a pure probe-tone at 226 Hz.<sup>4,5</sup>

One of the benefits of advanced technology in audiology is the ability to assess a wide frequency band using acoustic immittance measures or wideband tympanometry (WBT). Measuring a wide frequency band allows reflectance and absorbance values to be determined, depending on the device. Reflectance is defined as the sum of energy reflected by the middle ear over total energy in the auditory canal, with absorbance being the complement of reflectance. These measures have complementary values between 0 and 1, changing according to frequency and to the status of the tympano-ossicular system.<sup>6</sup> Both measurements have shown utility as diagnostic tools and can be readily measured across a broad range of frequencies using wideband stimuli.<sup>7-11</sup> Compared with traditional tympanometry, absorbance or reflectance measurements provide much more information on the state of the middle ear and allow more comprehensive assessment of middle-ear disorders.<sup>12,13</sup>

Many studies have shown reduced absorbance, or increased reflectance, in otosclerotic ears,<sup>14-19</sup> particularly in the low frequency band. This reduction in absorbance occurs due to increased stiffness in the system, which leads to a decreased acoustic sensitivity to low frequencies and, consequently, increased reflection. Thus, the energy absorbance measure can serve as an indicator of otosclerosis in suspected cases. The cited studies, however, were conducted only at ambient pressure, that is, without pressurization; only more recent studies analyzed pressurized WBT in otosclerosis.<sup>20,21</sup>

Analyzing acoustic absorbance at peak pressure can enhance its diagnostic value in disorders of the middle ear. The present study aims to map the amount of energy transferred to the system using wideband frequencies under ambient pressure and pressurized conditions. The study hypothesis is that the different anatomic conditions presented by the three groups studied have typical distinguishing features that can be measured using acoustic absorbance and employed to evaluate the effectiveness of stapedotomy.

Although much is known about otosclerosis, there are characteristics of the middle ear that warrant more in-depth study. Wideband tympanometry can measure how the middle ear absorbs sound over a much wider frequency band than conventional methods. The objectives of the present study were to use WBT to measure acoustic absorbance in patients with a diagnosis of fenestral otosclerosis pre and postsurgery, at ambient and peak pressure, to assess the effectiveness of stapedotomy.

## Method

The present cross-sectional prospective study was approved by the research ethics of the institution Irmandade da Santa Casa de Misericórdia de São Paulo. Data collection was performed between March 2016 and October 2017, and all participants signed a free and informed consent form.

The inclusion criteria for the study were patients of any gender aged >18 years old attending the outpatient clinic of the ENT Department, a public quaternary hospital, who had a clinically and computed tomography (CT)-confirmed diagnosis of fenestral otosclerosis and were indicated for stapedotomy or had previously undergone this surgery between January 2014 and October 2017 and were attending follow-up consultations. To be included in the control group, subjects had to have pure-tone behavioral audiometric thresholds better than 25 dB HL at octave frequencies between 250 and 8,000 Hz, report no history of middle-ear disease; and pass a transient-evoked otoacoustic emission (TEOAE) test. The TEOAE test protocol was performed with a TITAN device (Interacoustic, Middelfart, Denmark), using a non-linear click stimulus (frequency range 500–5,000 Hz) at an intensity of 80 dB peSPL. A pass consisted of a greater than 3-dB emission-to-noise ratio in 3 frequency bands (1,000, 2,000, and 4,000 Hz). The normal-hearing group consisted of undergraduates and staff from the institution. Individuals with a peak pressure, on conventional tympanometry, below -100 daPa, or other middle-ear disorders, such as simple chronic otitis media, were excluded from the study.

The data from 47 individuals were analyzed, for a total of 71 ears divided into 3 groups, as follows: presurgery group—diagnosed otosclerosis patients (22 ears); postsurgery group—otosclerosis submitted to stapedotomy (17 ears); and a control group—normal-hearing adults (32 ears).

The presurgery group had a mean age of 50 years, range 27 to 65 years, and comprised 13 women and 5 men. The postsurgery group had a mean age of 54 years (range 35 to 67 years) and included 7 women and 6 men, with a mean postsurgery time of 5 years (range 0.5 to 6 years) and no pharmaceutical protocol after the surgery. The control group had a mean age of 33.5 years and included 13 women and 3 men. The before and after surgery groups were comprised of different individuals.

In this study, according to the otosurgeon's notes from the stapedotomy surgery, all prostheses were made of Teflon, 0.6 × 6 mm. The team of supervisors at the ear surgery service has been the same for many years. The surgeries are performed in conjunction with residents, who vary each year.

Regarding the technique, the access is always transmeatic (or transmeatal), with the incision for the detachment of the tympanic-meatal flap performed just beyond the transition of the cartilage/bone portion of the external acoustic meatus. After confirming the fixation of the stapes/platinum to the oval window, the tendon of the stapes muscle is sectioned, the stapes incus disarticulated, and the stapes superstructure is removed. There are slight variations in technique depending on the preferences of the specific supervising surgeon (fenestrate before or after fracturing the cross and removing the superstructure, for example). However, whichever technique is used, at the end of the procedure, there is a folded tympanic-meatal flap, which is well positioned and intact, and an ossicular chain comprising the malleus, incus, and the 0.6-mm diameter teflon prosthesis positioned in the oval window, without any connection to the tendon of the stapes muscle.

### Equipment and Procedure

The device used in the study was a Titan handheld tympanometer (Interacoustics, Middelfart, Denmark), which was purchased using the FAPESP grant n° 2014/15810-0. The protocol defined for this study adopted the following set-up configurations:

- WBT module: 226 Hz to 8,000 Hz wideband stimuli; intensity: 100 dB SPL peak (adults); pressure: -600 to +300 daPa, using a standard Titan probe fitted with adaptable size latex olive ear tips. All tests were performed in a sound-proof booth by the same professional using the same device. The study protocol was applied after running basic audiometry tests and checking the study inclusion and exclusion criteria.

The WBT test provided the individual resonance frequency, conventional tympanometry results at 226 Hz, and also acoustic absorbance at frequencies in the 226-8,000 Hz range in two modalities: under ambient pressure and pressurized conditions.

The acoustic absorbance data of each participant were obtained using WBT research files on Microsoft Excel (Microsoft Corp., Redmond, WA, USA). The absorbance frequencies selected for analysis were based on data reported by Aithal et al.<sup>22</sup> The following frequencies were selected: 226 Hz, 257 Hz, 324 Hz, 408 Hz, 500 Hz, 630 Hz, 794 Hz, 1,000 Hz, 1,260 Hz, 1,587 Hz, 2,000 Hz, 2,520 Hz, 3,175 Hz, 4,000 Hz, 5,040 Hz, 6,350 Hz, and 8,000 Hz, amounting to a total of 17 frequencies analyzed per ear.

The data were analyzed by the statistics section of the institution, using descriptive analysis statistics techniques and the Mann-Whitney, Kruskal-Wallis, and Wilcoxon tests, with the SPSS Statistics for Windows, Version 13.0 (SPSS Inc. Chicago, IL, USA). The significance level of 5% was adopted for rejection of the null hypothesis.

### Results

Tympanometry data at 226 Hz obtained from the wideband tympanometry were classified according to Jerger.<sup>23</sup> The results were predominantly type A for both the control group

(100%) and the post-surgery group (94%). The presurgery group also predominantly presented type A curves (59%), followed by A's curves in 41% of cases.

The resonance frequency was registered from WBT under ambient pressure and pressurized conditions. The postsurgery-group showed the lowest resonance frequency at 1,000 Hz, followed by the control group, at 1,260 Hz, and, lastly, the presurgery group, at 1,587 Hz.

The mean absorbance values are presented in ►Table 1. The analysis of the acoustic data given in ►Fig. 1 shows that the control group had a wider and higher curve with greater acoustic absorbance values than the other 2 groups for all frequencies below 6,350 Hz. In the results of the tests performed under pressure, the postsurgery group had greater acoustic absorbance than the other 2 groups at 794 and 1,000 Hz, still with a left-shifted curve, whereas the right-shifted curve for the presurgery group showed higher absolute acoustic absorbance values than the postsurgery group, between 1,587 Hz and 6,350 Hz. The differences in absorbance in the 3 groups are presented in ►Table 2. ►Fig. 2 shows the acoustic absorbance, values are highlighted at ambient pressure and peak pressure by group and frequency. Although there was an improvement in hearing, surgery failed to restore the tympano-ossicular system to normal, as we can observe in the comparisons between the groups shown in ►Table 2.

### Comparison of Tests at Ambient Pressure Compared with Peak Pressure (Wilcoxon Test)

In the presurgery group, significant differences in tests at ambient pressure compared with peak pressure were found for 14 frequencies: 226 Hz, 257 Hz, 324 Hz, 408 Hz, 500 Hz, 630 Hz, 794 Hz, 1,000 Hz, 1,260 Hz, 2,000 Hz, 2,520 Hz, 3,175 Hz, 4,000 Hz, and 5,040 Hz ( $p < 0.03$ ).

In the postsurgery group, significant differences were found for 12 frequencies: 226 Hz, 257 Hz, 324 Hz, 408 Hz, 500 Hz, 630 Hz, 794 Hz, 1,000 Hz, 2,000 Hz, 2,520 Hz, 3,175 Hz, and 4,000 Hz ( $p < 0.03$ ).

In the control group, significant differences were found for 10 frequencies: 226 Hz, 257 Hz, 324 Hz, 408 Hz, 500 Hz, 630 Hz, 794 Hz, 1,000 Hz, 4,000 Hz, and 5,040 Hz ( $p < 0.02$ ).

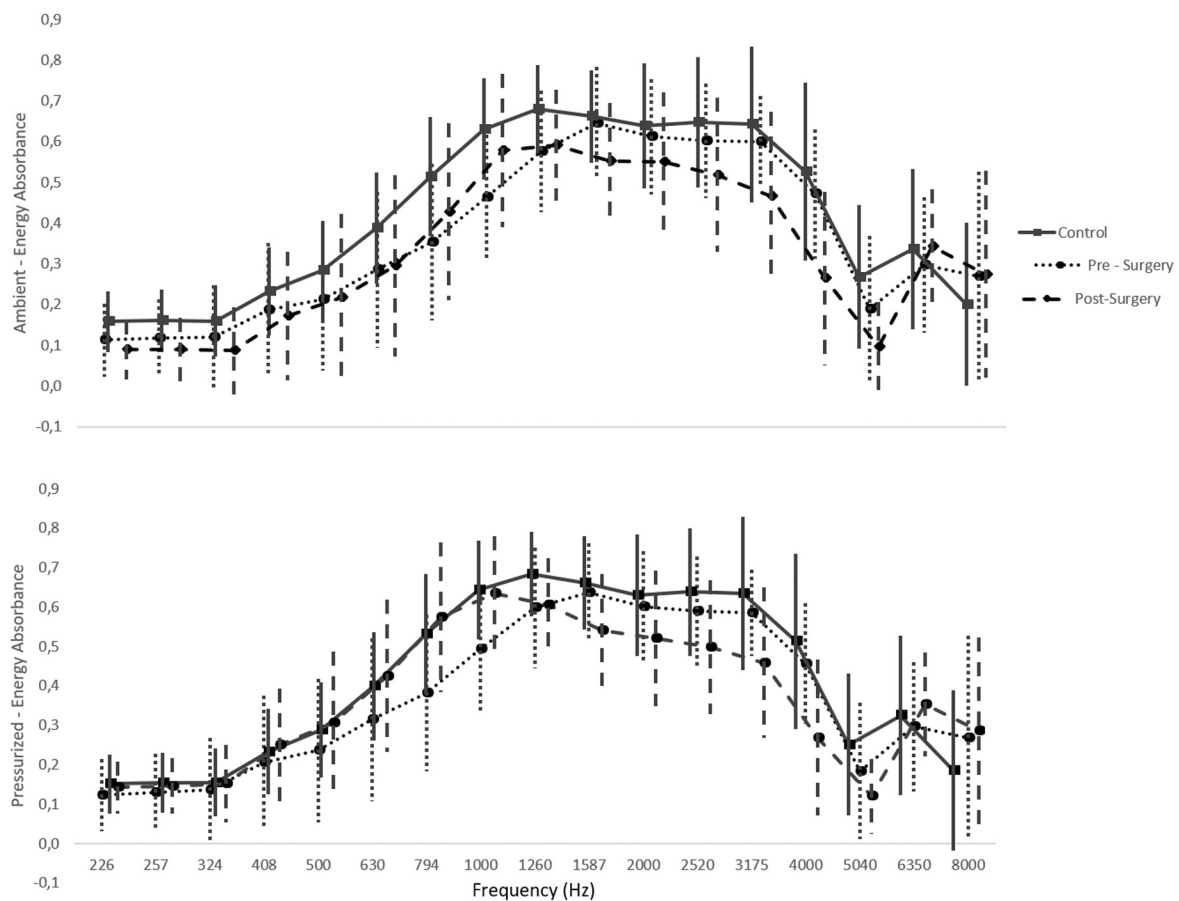
It is noteworthy to point out that, over the range from 226 Hz to 1,000 Hz, differences between pressurized and non-pressurized tests were found for all 3 groups. At higher frequencies, differences were evident between pressurized and non-pressurized conditions in the ranges 2,000 to 5,040 Hz for the presurgery group, 2,000 to 4,000 Hz for the postsurgery group, and 4,000 to 5,040 Hz for the control group.

### Discussion

The study of acoustic absorbance (using a wide frequency range and under different pressure conditions) in relation to middle-ear disorders has been the focus of growing research interest over the last decade. This interest prompted the present study, whose aim was to use WBT to characterize the physical condition of the middle-ear pre and postsurgical

**Table 1** Mean absorbance values by group and frequency at ambient and pressurized conditions

Frequency	Ambient absorbance			Pressurized absorbance		
	Control	Presurgery	Postsurgery	Control	Presurgery	Postsurgery
226	0.12	0.08	0.08	0.12	0.09	0.11
257	0.12	0.09	0.08	0.12	0.09	0.11
324	0.11	0.09	0.06	0.13	0.10	0.10
408	0.18	0.14	0.11	0.19	0.15	0.19
500	0.24	0.17	0.12	0.26	0.17	0.24
630	0.34	0.24	0.22	0.36	0.25	0.41
794	0.49	0.29	0.36	0.51	0.36	0.63
1,000	0.62	0.44	0.62	0.63	0.50	0.64
1,260	0.67	0.53	0.59	0.67	0.56	0.61
1,587	0.64	0.64	0.55	0.66	0.61	0.58
2,000	0.64	0.56	0.53	0.63	0.54	0.51
2,520	0.67	0.57	0.52	0.67	0.57	0.51
3,175	0.62	0.58	0.45	0.62	0.57	0.43
4,000	0.47	0.45	0.28	0.47	0.43	0.25
5,040	0.22	0.12	0.07	0.21	0.11	0.07
6,350	0.27	0.29	0.29	0.27	0.29	0.29
8,000	0.07	0.25	0.31	0.07	0.28	0.29



**Fig. 1** Comparison of mean acoustic absorbance values at ambient and pressurized conditions by frequency and group.

**Table 2** Assessment of significance of differences between absorbance of the groups (Mann-Whitney test)

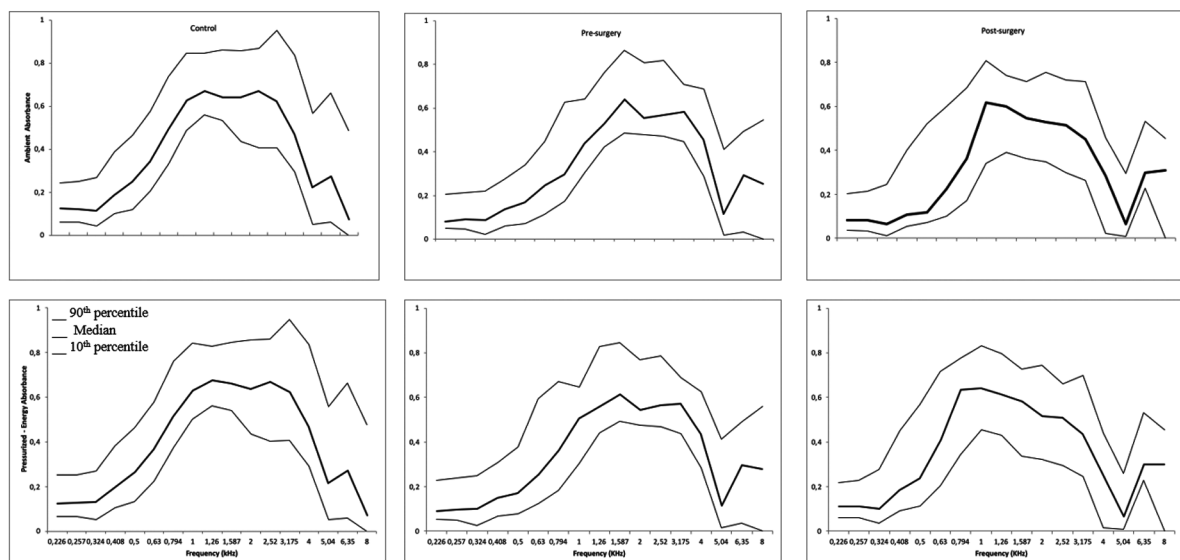
Frequency	Ambient absorbance			Pressurized absorbance		
	Control x Presurgery	Control x Postsurgery	Pre x Postsurgery	Control x Presurgery	Control x Postsurgery	Pre x Postsurgery
226	0.11	0.06	0.62	0.10	0.39	0.51
257	0.14	0.05	0.51	0.17	0.36	0.69
324	0.16	<b>0.04</b>	0.43	0.22	0.37	0.87
408	0.13	0.10	0.65	0.14	0.85	0.37
500	<b>0.04</b>	0.07	0.76	0.05	0.72	0.21
630	<b>0.00</b>	<b>0.04</b>	0.96	<b>0.02</b>	0.97	0.06
794	<b>0.00</b>	0.11	0.34	<b>0.00</b>	0.52	<b>0.00</b>
1,000	<b>0.00</b>	0.25	0.05	<b>0.00</b>	0.80	<b>0.00</b>
1,260	<b>0.00</b>	<b>0.01</b>	0.58	<b>0.00</b>	<b>0.02</b>	0.53
1,587	0.43	<b>0.00</b>	0.05	0.28	<b>0.00</b>	0.09
2,000	0.33	0.06	0.18	0.19	<b>0.03</b>	0.16
2,520	0.18	<b>0.01</b>	0.10	0.13	<b>0.00</b>	0.06
3,175	0.49	<b>0.00</b>	<b>0.01</b>	0.28	<b>0.00</b>	<b>0.01</b>
4,000	0.42	<b>0.00</b>	<b>0.00</b>	0.35	<b>0.00</b>	<b>0.00</b>
5,040	0.18	<b>0.00</b>	0.25	0.18	<b>0.00</b>	0.22
6,350	0.91	0.41	0.51	0.94	0.43	0.55
8,000	0.13	0.20	0.94	0.13	0.22	0.86

Note: Bold font was used to mark statistically significant differences ( $p < 0.05$ ).

intervention for otosclerosis to evaluate the effectiveness of stapedotomy. The study results confirmed the potential of acoustic absorbance measures to evaluate the impact of surgical procedures, as well as for diagnosing otosclerosis, differentiating it from similar conditions possibly associated with third window syndrome, such as superior semi-circular canal dehiscence. The results corroborate previous studies and include observations in respect of

pressurized acoustic absorbance, which has, to date, been little investigated.

The profile of the sample revealed that the mean age of the control group participants was lower than that of pre and postsurgery groups. However, resonance frequency in healthy middle ears does not change with age.<sup>24,25</sup> In addition, there were three times more females than males in the groups with otosclerosis, but this is consistent with the rates

**Fig. 2** Acoustic absorbance by frequency and group.

for the condition found in the literature, which show a higher prevalence of otosclerosis in females. Thus, the age and gender disparity between groups should be considered in the analysis of the results. Most individuals in the study group had bilateral otosclerosis, with only one subject having unilateral otosclerosis, corroborating reports that otosclerosis commonly affects temporal bones bilaterally.<sup>26</sup>

The acoustic absorbance data given in ►Figs. 1 and 2 illustrates the presence of a characteristic curve for each group investigated, differentiating them by ambient pressure and pressurized measurements. The results show higher resonance frequency values in otosclerotic ears compared with normal ears with significantly reduced absorbance for frequencies below ~2,000 Hz in presurgery group and significantly improved absorbance in that frequency range in the postsurgery group. After stapedotomy, the stiffness associated with otosclerosis is reduced, but compliance of the tympano-ossicular system is increased compared with normal ears, making resonant frequency even lower than normal.<sup>15,21,24,25,27</sup>

In the present study, testing of middle-ear resonant frequency revealed no difference between pressurized and non-pressurized conditions, where peak absorbance occurred at the same frequency for both pressure modalities. However, the configuration of the acoustic absorbance curve differed between these two modalities. In the presurgery group, the curve took on a wider shape under pressured conditions, associated with an increase in acoustic absorbance at 794 Hz and 1,000 Hz. In the postsurgery group, peak absorbance occurred at 1,000 Hz in the test at ambient pressure, but acoustic absorbance increased between 794 Hz and 1,000 Hz, forming a small plateau, and differentiating this curve from the control group curve over this frequency range.

Significant differences between the absorbance of normal and otosclerotic ears were found, especially at middle and low frequencies. No significant effect of ear side (right or left) or gender was observed. Less pronounced (although statistically significant) differences were found between normal and otosclerotic ears for average wideband absorbance and resonance frequency.

For all test conditions (ambient and peak pressure) and both ears presurgically, the frequency of 1,000 Hz was associated with low acoustic energy absorbance, a finding consistent with the literature which reports greater wideband acoustic reflectance at 1,000 Hz in subjects with otosclerosis.<sup>19</sup> Shahnaz et al.<sup>19</sup> compared the acoustic reflectance values of the middle-ear of individuals with surgically confirmed otosclerosis against data from normal-hearing individuals. Acoustic reflectance below 1,000 Hz was higher in otosclerotic than normal ears, and, thus, absorbance was lower at these frequencies, indicating that most of the energy under 1,000 Hz is reflected back to the external auditory canal, distinguishing otosclerotic from normal ears. These findings are consistent with the greater stiffness of the tympano-ossicular system. Conversely, higher absorbance at frequencies below 1,000 Hz and lower absorbance at frequencies above 1,000 Hz suggest less stiffness, such as

that induced by ossicular chain discontinuity. A more recent study by the same research group compared acoustic absorbance using multiple frequency tympanometry in otosclerotic ears pre and poststapedotomy. In the study, data from control ears and patient ears pre and postsurgery were analyzed, revealing a significant increase in acoustic absorbance in the middle ear at lower frequencies, in the range 226 to 1,000 Hz, after surgical treatment.<sup>28</sup>

Shanks and Shohet<sup>5</sup> essentially observed two tympanometry result patterns in otosclerosis: normal and stiff. These results are corroborated by the present study, that is, normal tympanometry curves for the control group and normal (A) or stiff (As) curves in the otosclerotic groups. At 226 Hz, the acoustic absorbance was extremely low across all three groups, as depicted in ►Figs. 1 and 2. In addition, no differences in acoustic absorbance values between groups and test pressure modalities were found. This result calls into question the reliability of tympanometry tests performed at 226 Hz, as is commonly done.

In the control group, the acoustic absorbance curve was similar at both ambient pressure and pressurized conditions, without clinical meaning. However, significant differences were found for 10 frequencies ( $p < 0.02$ ). Even though that control group had peak pressure close to zero (median -2.5 daPa), smaller negative middle-ear pressures could cause a significant change in reflectance, as demonstrated in Shaver & Sun (2013, JASA).<sup>29</sup> This result might be explained by the fact that, of the 3 groups studied, the postsurgery group had the lowest peak-pressure (median -21.00 daPa) and showed the most significant differences in the acoustic absorbance curve configuration according to pressure conditions (ambient and pressurized).

The average absorbance values for control group were in the range from 0.1 to 0.72 (10–20%), a figure similar to that previously reported in the literature. Liu et al.<sup>30</sup> reported normal values as lying in the range 0.1 to 0.9 (10–90%). The study found greater acoustic absorbance values for the normal-hearing population at 2,000 Hz, results echoed by the present study, in which highest peak absorbance was found for the frequency range 1,000 to 3,175 Hz under both ambient and pressurized conditions, and at peak pressure for both ears.<sup>30</sup>

A recent study<sup>15</sup> using the same equipment reported five types of absorbance plots in otosclerotic ears: type I, characterized by two distinct peaks; type II with a single distinct peak reaching high values of absorbance; type III, with reduced absorbance for frequencies < 1,000 Hz; type IV, with reduced absorbance for all frequencies; and type V, with reduced absorbance for frequencies > 2,000 Hz. Type II was the largest group found in this study,<sup>15</sup> and this was reinforced by the results found in the presurgery group in the present research. The same research group described that, in the postoperative group, mean absorbance in general was slightly increased after the surgical procedure, mainly at 226 to 2,000 Hz (the lower frequency band).<sup>21</sup> Their results are in agreement with those of the present study.

Regarding the measurement of peak pressure energy absorbance, another recent study reported that 650 Hz was

the optimum frequency range to differentiate otosclerosis. The test is highly effective, with a sensitivity and specificity of more than 85%.<sup>20</sup> In the present study, pressurized acoustic absorbance at 630 Hz can differentiate the control group from the presurgery group and the pre from the postsurgery group (–Table 2).

Absorbance measurements may play an important role in the diagnostics of otosclerosis; however, further research is necessary in this area. The present study had some limitations that should be noted, namely the small subject groups, and the lack of other tests to verify the results (e.g., audiometry). Also, the different surgical techniques used could have interfered in some way with the results; however, the differences were minimal, and the outcomes were similar, so this is unlikely. In addition to evaluating differences between normal-hearing and otosclerotic individuals, future studies could explore the possibility of using WBT as a tool for the differential diagnosis of conductive hearing loss. The study of physical characteristics of the middle ear in known situations is important to elucidate the physical dynamics. For example, without the influence of gas fluctuations, such as under normal conditions, in the presence of stiffness secondary to otosclerosis, and in ears with the stapes and ligament removed.

Moreover, accurate characterization of the properties of ears with fenestral otosclerosis can be useful in differential diagnosis with other diseases that cause conductive hearing loss, such as superior semicircular canal dehiscence. It is known that 7.7% of individuals with this syndrome report no vertigo,<sup>31</sup> with audiometry disclosing an air-bone gap at low frequencies and stapedius muscle reflex on conventional tympanometry. Currently, the complementary tests employed to differentiate the two conditions are vestibular evoked myogenic potential (VEMP) testing and high-resolution computed tomography. The wideband tympanometry test can be of great utility in differentiating these two diseases, offering greater simplicity and speed over the other techniques mentioned. Other pathologies of the middle ear that are more common than superior semicircular canal dehiscence and with less specific findings on complementary exams, such as ossicular chain dislocation with or without mucosa bridge, tympanic membrane hypermobility, tympanosclerosis and other cicatricial diseases, could be differentiated from otosclerosis on the basis of WBT findings,<sup>32</sup> making this test an option for investigating conductive hearing loss.

## Conclusion

In summary, the three groups studied showed distinctive patterns of WBT, under both ambient and pressurized conditions, disclosing greater stiffness in otosclerotic ears. Thus, wideband absorbance was able to distinguish pre and postsurgery otosclerotic ears from normal ears. The study showed encouraging results in relation to stapedotomy, with the absorbance of frequencies below 2,000 Hz significantly improved in the postsurgery group. However, al-

though the surgery improved hearing, it failed to restore the tympano-ossicular system to normal.

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## Conflict of Interests

The authors have no conflict of interests to declare.

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