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The tympanic membrane displacement test and tinnitus: preliminary report on clinical observations, applications, and implications

Abraham Shulman[1]
Barbara Goldstein[2]
Robert J. Marchbanks[3]

Abstract

The tympanic membrane displacement test (TMDT) is an attempt to record intracranial pressure (ICP) reflective of an intracranial pulse pressure amplitude wave (IPPA) transmitted to the inner ear and tympanic membrane with a probe placed into the external ear canal. Twelve tinnitus patients, divided into two groups, who were resistant to attempts to achieve tinnitus control or relief were selected for the TMDT. The group 1 TMDT recordings were obtained on one session test date, and group 2 (n = 6) recordings were obtained sequentially on different session test dates. Patient selection with the medical audiologic tinnitus patient protocol (MATPP) identified all to have a nonpulsatile, predominantly central-type severe disabling subjective idiopathic tinnitus (SIT) resistant to attempts for tinnitus relief with instrumentation or medication. Associated complaints in all selected SIT patients included persistent ear blockage in the SIT ear, normal middle-ear function, controlled secondary endolymphatic hydrops in the SIT ear, sensorineural hearing loss of high frequency, hyperacusis, occasional vertigo, and central nervous system complaints of headache, head pressure, and cognitive interference in memory and/or speech expression. Clinical concern is for the presence of an increased ICP reflecting an idiopathic intracranial hypertension (IIH) which, if not identified and treated, may be a factor influencing the clinical course of this particular cohort of SIT patients, highlighted by persistent ear blockage and associated complaints as described. **Objectives:** We set out to accomplish a number of goals: (1) To identify abnormal intracranial pulse pressure (IPPA ICP) with the extracranial TMD in a preselected particular cohort of SIT patients clinically suspected (by use of the MATPP) to have an abnormal ICP (i.e., IIH); (2) to identify the abnormal IPPA ICP as a positive indicator for IIH and as a factor - not an etiology - influencing the clinical course of SIT in a preselected cohort of SIT patients; (3) to identify with the TMDT in SIT patients spontaneous nonevoked recordings of intra-aural pressure and test-retest reliability of the TMDT; (4) to identify with the TMDT levels of normal and abnormal IPPA ICP in real time in the clinical course of SIT (i.e., an objective diagnostic and treatment monitor function of the TMD targeting ICP and IIH before and after treatment); (5) to attempt to establish a correlation of treatment efficacy, targeting pre- and post-ICP as a manifestation of IIH, with SIT subjective tinnitus relief; (6) to identify the limitations and complications of the TMDT; and (7) to share with the reader the evolution of a new science of brain pulsatility and a technology having a clinical application for otology and neurotology complaints of hearing loss, tinnitus, ear blockage, and vertigo. The results reported in the literature complement and alter conventional medical teaching focusing on brain pulsation, absolute intracranial pressure, and brain disease. **Method:** The Southampton Tympanic Membrane Displacement Analyzer was used to record spontaneous intra-aural pressure waves in 12 SIT patients. Patients selected for the TMDT were divided into two groups: Group 1 (n = 6) recordings were obtained on one session test date, and group 2 (n = 6) recordings were obtained sequentially on different session test dates. Multiple recordings were attempted in all patients to identify test-retest reliability in both groups. An attempt for treatment and control of an elevated ICP with or without reduced cerebral compliance (CC) was recommended in 4 patients. **Results:** With single and multiple recordings using the TMDT, the IPPA (i.e., ICP) was demonstrated to be abnormal and to fluctuate in the clinical course of 10 of the 12 predominantly central-type tinnitus patients (SIT): abnormal IIPA with reduced CC in 8 of 12 patients and normal IPPA with reduced compliance in 2 of 12. Tinnitus treatment results targeting ICP as a manifestation of IIH with Diamox were positive in the short term in 2 patients and incomplete in 3. The SIT relief is reflective of fluctuation in the ICP and the overall issue of multifactorial brain pulsatility. **Conclusions:** (1) The TMDT demonstrated repeated and consistent spontaneous nonevoked recordings of displacement of the tympanic membrane, reflective of intra-aural pressure, abnormal IPPA ICP in a preselected particular cohort of SIT patients clinically suspected to have an abnormal ICP (i.e., IIH). (2) Test-retest reliability of the TMDT was positive. (3) The results of the TMDT application for identification of an elevated ICP and reduced CC were positive in 10 of 12 particular preselected patients with nonpulsatile, predominantly central-type SIT resistant to attempts for tinnitus relief with instrumentation or medication. These positive findings support clinical and basic science investigations previously reported in the literature. (4) The clinical significance of these preliminary results of an elevated ICP in a particular cohort of SIT patients supports the clinical impression of the presence of an IIH and its influence on the clinical course and overall treatment of SIT. (5) A final conclusion as to the clinical significance of an elevated ICP and reduced CC for IIH and the diagnosis and treatment of tinnitus remains to be established.

Keywords: autoregulation cerebral compliance, idiopathic intracranial hypertension, intra-aural pressure waves, intracranial pressure, intracranial pulse pressure amplitude, tympanic membrane displacement test.

[1] Professor Emeritus, Clinical Otolaryngology, SUNY - Downstate Medical Center, and Director of Otology/Neurotology, Martha Entenmann Tinnitus Research Center, Inc., Brooklyn, NY.
[2] Assistant Clinical Professor, Department of Otolaryngology, SUNY - Downstate Medical Center, and Director of Audiology, Martha Entenmann Tinnitus Research Center, Inc., Brooklyn, NY.
[3] Consultant Clinical Scientist, Neurological Physics Group, Medical Physics, University Hospital Southampton, NHS Foundation Trust, UK.

Robert J Marchbanks. PhD, is managing director of Marchbanks Measurement Systems Ltd., a spinoff company from Southampton University that supports research with the Tympanic Membrane Displacement Analyzer.

INTRODUCTION

The complaint of subjective ear blockage (EB) is frequently associated with subjective idiopathic tinnitus. Site(s) of lesion include, but are not limited to, frequent obstruction in the external ear canal, interference in eustachian tube function and aeration of the middle ear(s), and endolymphatic hydrops (EH) of the inner ear. For the subjective idiopathic tinnitus patient, the evaluation of a persistent subjective complaint of EB, in the absence of a site of lesion in these frequent locations, has been hypothesized since 1979 to reflect a fluctuation or elevation of intracranial pressure (ICP)[1-3].

In our evolving clinical tinnitus experience since 1979, at SUNY-Downstate Medical Center and the Martha Entenmann Tinnitus Research Center, in excess of 15,000 patients have been seen in neurotologic-audiologic consultation in whom different clinical types of tinnitus - predominantly a central-type severe disabling subjective idiopathic tinnitus (SIT) - have been identified with a medical audiologic tinnitus patient protocol (MATPP)[4].

In general, a significant associated complaint in SIT patients has been of ear blockage of fluctuant intensity located in the ear(s) with the SIT complaint. Additional significant ear complaints have included vertigo, high- and ultra-high-frequency sensorineural hearing loss greater than expected for the age of the patient, and hyperacusis.

Our interest in the tympanic membrane displacement test (TMDT) and ICP and idiopathic intracranial hypertension (IIH) has paralleled, since 1979, an increasingly frequent clinical experience with SIT patients in whom the following conditions are present: (1) persistent complaint of ear blockage after control of eustachian tube obstruction or secondary EH (SEH) and (2) a reduced vestibular response with caloric, sinusoidal, harmonic rotary-chair testing or the Fukuda stepping test in the absence of subjective vertigo in the SIT ear. The MATPP identified the ear blockage to be obstruction in the external ear canal, interference in eustachian tube function and aeration of the middle ear(s), or SEH of the inner ear. The blockage persisted in the SIT ear following control of the clinically identified site of lesion of the blockage. Our experience with SEH has been reported[5]. In this cohort of SIT patients, the ear blockage persisted after treatment of SEH in the SIT ear. Notable additional associated complaints are head pressure, headache, and cognitive complaint(s) of interference in memory and speech expression - in short, a combination of ear and brain function complaints. In this cohort of SIT patients, in whom the complaint of ear blockage is marked, experience has been limited with, or patients have proven resistant to, attempts at tinnitus relief with medication and instrumentation targeting conditions in ear or brain identified with the MATPP to influence the clinical course of SIT.

Our introduction to the TMD occurred in 2005, at the Fifth International Symposium: Ménière's Disease and Inner Ear Homeostasis Disorders, House Ear Institute, Los Angeles, CA. Among the presentations were "Intracranial Pressure Waves and Inner Ear Homeostasis Disorders" by Robert J. Marchbanks and "Ménière's Disease, Secondary Endolymphatic Hydrops, and Tinnitus" by Abraham Shulman. Discussions after our presentations allowed us to share our evolving experiences with SIT and TMDT and to consider the potential role of TMD and brain pulsatility for SIT in general and for SEH specifically. At that time, we planned our TMDT collaboration, which has been ongoing since 2007[6].

We have reported since 2006 our clinical experience with SIT in terms of the fluid dynamics between ear and brain, brain and inner ear fluid homeostasis, cochlear- or vestibular-type tinnitus, and SEH[7]. This ongoing clinical experience has been the basis for the fluid dynamics vascular theory of brain and inner ear function in traumatic brain injury as a translational hypothesis for the diagnosis and treatment of SIT[8].

It has been hypothesized that persistence of the complaint of ear blockage in the SIT ear with maintenance and control of function in the external or middle and inner ear reflects an alteration in fluid dynamics between the ear and brain, a biologic marker being alteration or elevation of ICP, reflecting IIH, highlighted by the complaint of ear blockage. Introduction of the TMDT into the MATPP in selected patients may be a technological advance for identification and treatment of ICP and identification of IIH for a particular cohort of SIT patients with the etiologies of inflammatory disease; noise exposure; physical trauma involving the middle ear, inner ear, and brain; and central nervous system (CNS) neurodegeneration. Identification and treatment or control of ICP may be a factor influencing the clinical course, in general, of all clinical types of tinnitus and, in particular, of this cohort of SIT patients. The result may be increased efficacy for tinnitus relief with existing modalities of instrumentation or medication[9-11].

This preliminary report includes a brief introduction to the TMDT technique and the results of the TMDT in two groups of SIT patients for (1) identification of abnormal intracranial pulse pressure amplitude (IPPA) in a preselected SIT population clinically suspected for an abnormal IPPA; (2) identification of IPPA as a factor influencing the clinical course of SIT in a preselected cohort of SIT patients; (3) identification of the test-retest reliability of TMD; (4) evaluation of the levels of normal and abnormal IPPA ICP in real time in the clinical course of the SIT (i.e., an objective monitor function for ICP as a manifestation of IIH before and after treatment); and

(5) identification of limitations and complications of the TMDT. In addition, this article shares with the reader the evolution of a new science of brain pulsatility with application for otologic and neurotologic complaints of hearing loss, tinnitus, ear blockage, and vertigo, which complements conventional medical teaching focusing on brain pulsation, absolute ICP, and brain disease. A case report will demonstrate the result of translation of an elevated ICP for tinnitus treatment on the clinical course of the SIT patient.

HYPOTHESIS

Abnormal intracranial pressure (i.e., IPPA ICP) and its fluctuation is a factor related to the clinical course of a subgroup of SIT patients. The abnormal ICP is clinically suspected to be the manifestation of an IIH. Animal and human results of identification of ICP with an external probe device in the ear canal, recording tympanic membrane displacement, reflective of the IPPA and its modulation by respiration, may be translated for this subgroup of SIT patients. The identification and translation for treatment and control of ICP as a manifestation of IIH may influence the clinical course of this patient subgroup. A patient selection process is recommended to identify this patient subgroup.

HISTORICAL BACKGROUND

IIH, TMDT, and tinnitus

The experience with the TMDT for the diagnosis of IIH associated with tinnitus, also referred to as *benign intracranial hypertension* and *pseudotumor cerebri*, has been reported. Headache, chronic fatigue, "brain fog," tinnitus, visual obscurations, dizziness, and sometimes hearing loss are the principle symptoms of IIH. Significant for this publication are the reported findings that "low-frequency and/or pulsatile tinnitus may be the single most distinct indicator of IIH" and that "the characteristic low-frequency tinnitus found with IIH is postulated to be caused by fluid turbulence within the cochlear aqueduct, which, in some cases, causes EH owing to disturbances of the intracranial-labyrinthine fluid dynamics"[12].

Intracranial hypertension was reported in 1981 to become manifest with neurotologic symptoms: The most common presenting symptom was pulsatile tinnitus, followed by hearing loss, dizziness or vertigo, and aural fullness[13]. The most common etiology was benign intracranial hypertension syndrome (pseudotumor cerebri). Sismanis[14,15] noted that "pulsations of the cerebrospinal fluid, mainly originating from the circle of Willis, are transmitted to the exposed medial aspect of the venous sinuses (transverse and sigmoid), resulting in periodic compression to their walls. These periodic compressions convert the laminar blood flow into turbulent flow, resulting in vibrations of the vessel walls and production of pulsatile tinnitus".

Historically, the clinical application of the TMD for measurement of ICP is supported by animal, human, basic science, and clinical investigations. The question of whether papilledema in the eye, and inner-ear complaints, including ear blockage, hearing loss, and vertigo, are analogous manifestations of an elevated ICP is not new. An excellent summary of past efforts since 1924 both in animal and humans concluded that alterations in ICP can explain some inner-ear complaints including hearing loss, tinnitus, and vertigo. This same report supported the existence of an "obligatory" interrelationship between ear and ICP[16].

Clinically, the publications cited in the next section support the hypothesis that an abnormal and fluctuating ICP is a factor related in the clinical course of a previously described subgroup of SIT patients. Identification and treatment of this abnormal ICP may improve diagnostic accuracy and treatment for this particular cohort of SIT patients.

TMD and intracranial, perilymphatic, and endolymphatic pressures

Of the two fluids within the cochlea, the endolymph and the perilymph, it is the perilymph that interfaces with the footplate, and it is the pressure of this fluid that is assessed by the Cerebral and Cochlear Fluid Pressure Analyser and the TMDT technique. Both fluids are "referenced" to the same pressure, that of the intracranial fluid. The cochlear aqueduct is the main fluid communication route between the intracranial and perilymphatic fluids; it runs from the subarachnoid space and enters the cochlea in a niche just near the round window[17-19].

Proof of intracranial measurements by TMD (evoked TMD): animal studies

Labyrinthine pressure and cerebrospinal fluid pressure

In the guinea pig, Böhmer[20] reported that "the endolymph indirectly communicates with the intracranial fluids via the endolymphatic sac and maintains homeostasis with the perilymphatic pressure across the Reissner's and other intralabyrinthine membranes. Positive endolymphatic-perilymphatic pressure gradients are secondary to and not the primary cause of hydrops formation. In experimental EH, deterioration of auditory thresholds was partially correlated to the presence of positive endolymphatic-perilymphatic pressure gradients. A change in pressure, however, occurred later than the first deterioration in auditory function. Therefore, positive endoperilymphatic pressure gradients may contribute to, but are not the only cause of, hearing impairment".

Perivascular or perineural routes between the intracranial and labyrinthine spaces may also provide a means of communication, but these may be significant only in cases of extremely elevated ICP or certain malformations. Experiments in the cat have demonstrated that labyrinthine pressure mirrors that of the cerebrospinal fluid (CSF) and that no change in labyrinthine pressure can be measured if the cochlear and vestibular aqueducts are sealed[21,22].

Clinical analysis of a trial of ICP measurement from the external auditory canal concluded that intra-aural pressure waves clearly reflect intracranial cardiovascular and respiratory pulsatility changes in cats[23].

Induced longitudinal endolymph displacements by infrasound (guinea pig)

In a guinea pig model, infrasound (0.1-10 Hz) within the perilymph induced longitudinal sinusoidal and gross displacement of the endolymph. Though the displacements are very small, they cause a large endocochlear potential change (> 20 mV)[24]. Acute EH was generated by exposure of the guinea pig ear to nontraumatic low-frequency tone[25]. A 3-minute, 200-Hz tone at 115 dB was sufficient to generate an acute EH condition in 29 guinea pigs[25].

Hydrops in the cochlea can be induced by sound as well as by static pressure. Reissner's membrane was visualized by confocal microscope in an isolated temporal bone of a guinea pig. The function of the organ was followed by measuring its physiologic response after applying static pressure and repeated tone bursts of more than 80 dB[26].

Proof of intracranial measurements by TMD (evoked TMD): human studies

Varying patency of the cochlear aqueduct and connectivity to the perilymphatic space of the cochlear labyrinth of the inner ear in human temporal bones was reported by Wlodyka[27]. Cochlear aqueduct patency is known to be reduced with increasing age, falling to 50% in subjects older than 40 years and 30% in those older than 60.

Pressure and flow pulsatility can change with disease. In brain, a pressure volume curve has been described based on the exponential pressure - volume relationship in the cranium. The changes in pulsatility (i.e., cardiac-induced pulsatility) are predominantly due to the dependence of volume change on mean pressure[28].

Testing in normal subjects shows that stable TMDT results are obtained during the day and after exercise[28]. These normative data also demonstrate large intersubject differences; nevertheless, the correlation of test results within one individual is high. From this, it is concluded that the TMDT gives the optimum results when testing for pressure changes within the same individual, such as changes that may occur with symptoms or treatment[30,31].

Evidence for intra-aural pressure waves of intracranial origin (spontaneous TMD)

Marchbanks[17] hypothesized that ICP could be measured intra-aurally. Intra-aural pressure waves of intracranial origin may cause oscillopsia[32]. A trial of ICP measurement from the external auditory canal concluded that intra-aural pressure waves clearly reflect intracranial changes in humans, thus proving Marchbanks's hypothesis[33].

Noninvasive intracranial compliance monitoring by measurement of intra-aural pressure waves, performed on neurosurgical patients, has identified certain characteristics of the intra-aural pressure pulse that may allow for noninvasive measurement of ICP and compliance[34,35].

The Southampton Tympanic Membrane Displacement Analyzer, commercially available as the MMS-11 Cerebral and Cochlear Fluid Pressure (CCFP) Analyser, is able to measure extremely small displacements of the tympanic membrane pressure pulses at heartbeat and respiration frequencies that are transmitted from the intracranial pulse pressure to the tympanic membrane (Figure 1). The TMD displacements are intra-aural waves of different morphologic types, measured in nanoliters and in milliseconds of time, reflective of the pulsatility in brain. The cardiovascular component is the predominant waveform, modulated by the respiratory component. The various characteristics have been categorized into four distinct types (Figure 2). Type 1 shows extraordinarily large pressure waves that are synchronous with the heartbeat. In agreement with accepted CSF mechanics, these pressure waves are seen to increase in amplitude as the mechanical compliance of the CSF system declines with increasing ICP. Types 2 and 3 are intra-aural pressure waves that are associated with respiration; in type 3, the amplitude of the cardiovascular pulse varies with the phase of the respiration. The type 4 intra-aural pressure wave has been named the *M wave*, is of unknown origin, and was not demonstrated at this time. Measurement of the IPPA of the cardiovascular component is the objective measurement of the ICP and perilymphatic cochlear pressure.

The tympanic membrane in humans is constantly in motion, principally of cerebral cardiovascular and respiratory origin. In most people, a fluid connection exists between the intracranial fluid and the fluids of the inner ear. The MMS-11 CCFP Analyser is used to provide an indirect measure of baseline (static) cerebral and cochlear pressures by the detection of low-frequency pressure waves that are emitted from

the ear, a component of which is of intracranial origin. An ear probe inserted into the ear canal of the ear to be tested is connected to the analyzer. Diaphragm movements in the sensor attached to the probe track tympanic membrane movements to record the tympanic membrane displacement, which is recorded as a volume displacement and is reflective of the ICP.

The ICP wave measurements can be obtained in two modes of operation: In the first, a TMD is *evoked* using the acoustic stapedial reflex. Baseline ICP is extrapolated based on the evoked TMD. Clinically, increased ICP reflects intracranial hypertension, whereas low pressure reflects intracranial hypotension. In the second operational mode, TMD is *spontaneous*: That is, baseline ICP is extrapolated based on measurement of the ongoing spontaneous displacement of the tympanic membrane, hypothesized to be reflective of ICP waves principally of cerebral cardiovascular and respiratory origin.

The mechanism of the TMD is hypothesized to be a reflection of increased ICP and perilymphatic pressure on the acoustic stapedial reflex and its action on the stapes footplate, ossicular chain, and tympanic membrane. Increased ICP results in increased perilymphatic pressure**,** outward resting position of the stapes footplate, and inward movement of the tympanic membrane on reflex contraction of the stapedial muscle. Reduced ICP results in an inward resting position of the stapes footplate and outward displacement of the tympanic membrane on muscle contraction.[17] Measurements appear to reflect cerebral autoregulation in some cases. Fine detail can be resolved on the tympanic pressure pulses.

The TMDT is postulated to provide a "signature" of the underlying neurological disorder in terms of CSF hydrodynamics[36].

METHOD

Patient selection

The patient selection protocol included (1) identification with the MATPP of a nonpulsatile, predominantly central-type, severe disabling subjective idiopathic tinnitus (SIT) resistant to attempts for tinnitus relief with instrumentation or medication; (2) persistent ear blockage and controlled SEH in the SIT ear; (3) normal middle-ear function; (4) sensorineural hearing loss at high- and ultra-high-frequencies; (5) hyperacusis; (6) occasional vertigo; and (7) CNS complaints of headache, head pressure, and cognitive interference in memory or speech expression (or both). Exclusion patient criteria included all clinical types of tinnitus not classified as SIT, obstruction in the external ear canal, active middle-ear or inner-ear disease, and pregnancy**.**

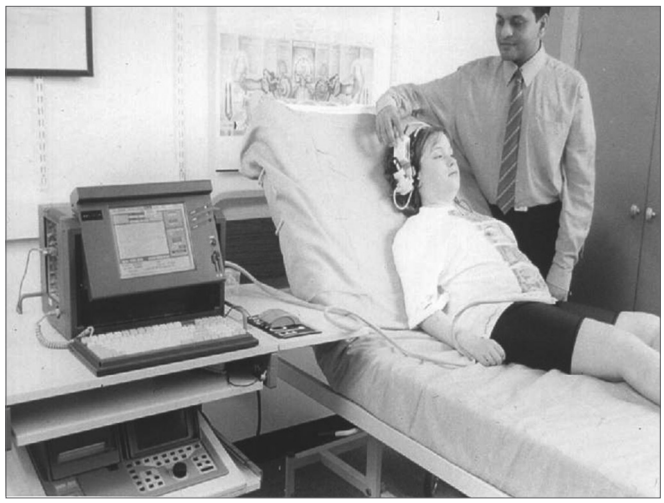

Figure 1. The Southampton Tympanic Membrane Displacement (TMD) Analyser. Patient reclining on a bed, supine in a 45-degree position for recording of IPPA. A recording probe in place in the right ear canal and maintained with a head band. The doctor is standing to the patient's left. The equipment is in two boxes.

All patients selected according to the preceding protocol (n = 12) between July 2007 and March 2012 underwent a neurotologic examination of the head and neck, including microscopical examination of the ear canals and tympanic membrane for evidence of pulsation and auscultation of the ear canals, head, and neck. The tinnitus evaluation included pure-tone air and bone conduction, 250- to 8000-Hz speech audiometry, tympanometry, and ultra-high-frequency audiometry. Vestibular caloric and sinusoidal harmonic rotary-chair testing was performed on all SIT patients. Opthalmoscopic examination of the eye was performed on all SIT patients.

The 12 selected patients were further classified into two groups, the first group of 6 patients undergoing the TMDT on a single date and the second group of 6 undergoing TMD on sequential test dates. All patients were males aged 30-72 years who were resistant to conventional attempts for tinnitus relief with instrumentation or medication, and all were hypothesized to have a possible increased ICP based on associated clinical complaints and findings. Magnetic resonance imaging of brain with contrast reported no significant CNS pathology, with only occasional white matter changes, in 10 of the 12 subjects in this study.

Among the associated complaints and findings were the following:

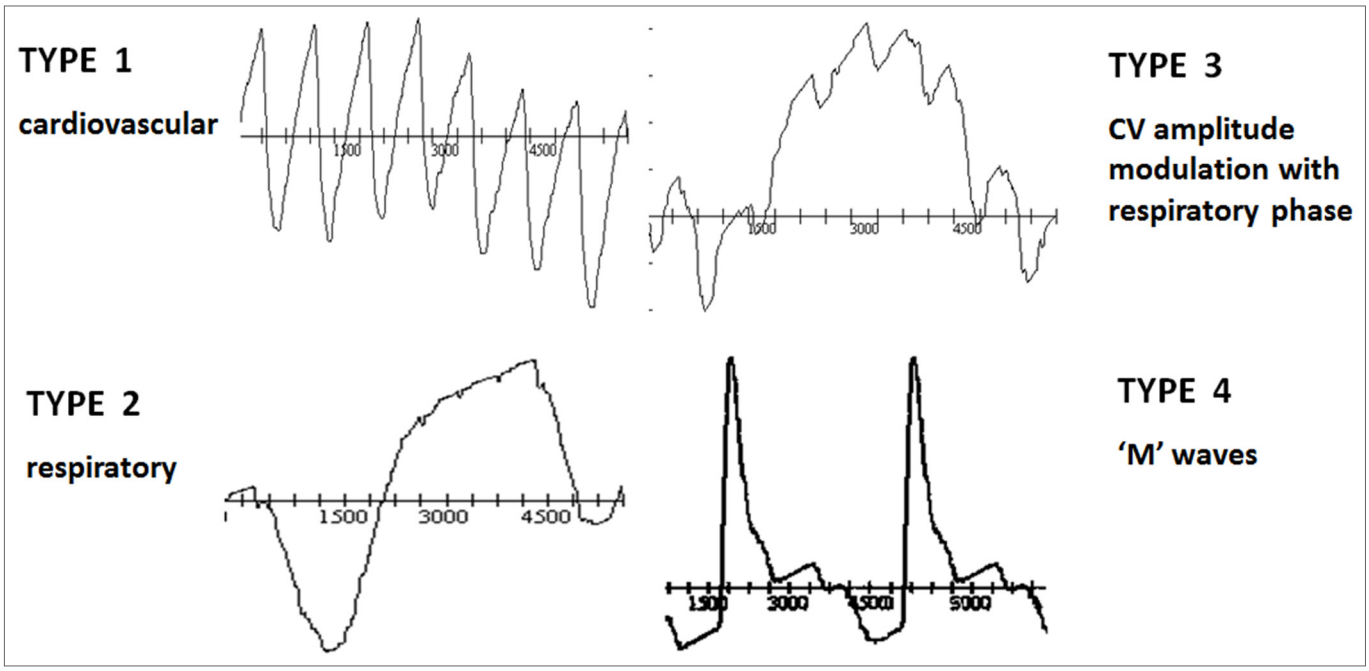

Figure 2. Intra-aural pressure waves of intracranial origin - morphometric types. (CV = cerebrovascular).

- Persistent ear blockage in the SIT ear or head pressure or both;
- Sensorineural hearing loss in the conventional high (4-8 kHz) and ultra-high frequencies (10-20 kHz);
- Normal tympanometry;
- Normal middle-ear function;
- Absent or controlled SEH in the SIT ear;
- Clinical symptoms reflective of interference in brain function (memory, cognition, speech expression); and
- Abnormal results on quantitative electroencephalography (QEEG).

Neurotologic and otologic physical examination identified integrity of the external ear canal and tympanic membrane with no spontaneous signs of labyrinthine irritation. Immitance testing with the Grason Stadler Portable Handheld Tympanometer (Grason Stadler Eden Prairie, MN) revealed normal type A tympanograms.

TMD recordings were obtained in the two groups of patients to observe the temporal course of the ICP in SIT. The tests were performed with the CCFP Analyser to obtain recordings of the waveforms of spontaneous displacement of the tympanic membrane accompanying testing in three positions - supine, 30-degree, and 45-degree - and reverse. Ten spontaneous, repeated, binaural 20-sec recordings were obtained in all patients. Duration of the procedure was 20-30 minutes.

The evoked TMD was not performed. The concern was a potential increase in SIT owing to the intensity of sound stimulation recommended to elicit the evoked acoustic stapedial reflex (i.e., 1 kHz/300 ms/15 dB above reflex threshold = 80-90 dB to 100-110 dB).

Data analysis

ICP is normally 7-15 mm Hg for a supine adult and becomes negative (averaging-10 mm Hg) in the vertical position. At 20-25 mm Hg, the upper limit of normal, treatment to reduce ICP may be necessary[37].

- Intracranial pulse pressure amplitude IPPA
  - Normal, reflective of ICP: cardiovascular pulse amplitude < 500 nl peak to trough
  - Abnormal: cardiovascular pulse amplitude > 500 nl peak to trough
- Cerebral compliance (normal cardiovascular amplitude and normal cardiovascular pulse modulation with respiration)
  - Normal: < 400 nl
  - Borderline: 400-500 nl
  - Abnormal: > 500 nl = reduced CC = abnormal cardiovascular pulse modulation of > 80% and/or abnormal cardiovascular pulse amplitude
- Conversions
  - TMD 500 nl = 5 mmHg
  - Normal CSF = 4.4-7.3 mmHg, 100-200 mm H_2O
- Normative database reference: Southampton University normative adult females, 60 subjects, aged 18-55 years

TMD RESULTS

The TMDT results in group 1 (n = 6) (Figure 3) and group 2 (n = 6) (Figure 4) are reported in five waveform categories labeled *A* to *E*, as follows:

A Normal IPPA
B Abnormal IPPA
C Normal CC
D Reduced CC
E Incomplete

In the two groups, 10 of 12 patients exhibited abnormalities on TMDT. Eight fell into the B and D waveform categories (abnormal IPPA and reduced CC), whereas two fell into the A and D waveform categories (normal IPPA and reduced CC). Of the 12 patients, 2 were classified into category E. These two incomplete TMD recordings were associated with an inability to maintain an adequate seal of the probe in the ear canal.

Case report: patient 2.1

The subject of this case report is a 71-year-old white man with SIT, the quality of which was a high-pitched "ee" of constant duration located in the left ear. Audiometric evaluation (250-8000 Hz) revealed symmetrical 4- to 8-kHz high-frequency sensorineural hearing loss; 10- to 20-kHz ultra-high-frequency hearing loss to the limits of the audiometer (120 dB SPL) that was severe to profound in both ears. The tinnitus evaluation identified SIT, masking curve type 4; and an abnormal result on QEEG.

Associated complaints included hypertension, left-ear blockage that fluctuated with tinnitus intensity, nasal allergy, occasional unsteadiness, occasional frontal headache, head pressure, memory interference, and occasional delay in speech expression. Left-ear blockage persisted after allergy evaluation and treatment. Bilateral type A tympanograms were obtained with immittance testing. MRI of brain revealed flair/T2 sequences, nonspecific periventricular white matter changes, and global mild to moderate volume loss consistent with the patient's age.

The patient demonstrated a fluctuating ICP with sequential TMD testing between July 2007 and March 2012, prior to and after treatment with Diamox (Figures 4, 5). Diamox was recommended after increased ICP was identified in July 2007. Amplitude and modulation of the cardiovascular pulse by respiration varied over time. Abnormal amplitude and modulation were reported in July and September 2007, November 2008, and March 2012, concurrent with subjective reports of elevated intensity of the patient's SIT. The TMDT recordings during the span between October 2007 and March 2012 reflect the clinical course of the SIT prior to and after intake of Diamox 250 OD, which occurred following September 2007 (i.e., October 2007-March 2012; see Figure 5). The 2007 to 2012 TMDT recordings demonstrated (1) normal amplitude of the cardiovascular pressure wave (IPPA) with abnormal modulation by respiration and reduced CC in October 2007 and (2) fluctuation of CC (reduced and abnormal in October 2007 and August 2008, normal in November 2007, and abnormal in March 2012).

Significantly, objective improvement was noted in the TMD recording from abnormal IPPA ICP to normal, as noted in the elevated amplitude between July and September 2007 and in the normal IPPA amplitude and modulation by respiration between October 2007 and August 2008. This objective improvement correlated with a reported subjective reduction in SIT intensity, which continued with fluctuation until March 2012. The TMDT at that time demonstrated an abnormal ICP as measured by an increased IPPA amplitude and normal modulation by respiration, with a reduction in compliance, which correlated with

Recording dates	7/07	9/07	10/07	11/07	3/08	8/08	11/08	4/09	3/12
Group 1 Subjects, Single Recording									
(1.1)								B,D	
(1.2)								B,D	
(1.3)								E	
(1.4)								A,C	
(1.5)									B,D
(1.6)									A,D

Figure 3. Tinnitus summary, group 1: Tympanic membrane displacement (TMD) in a cohort of patients with nonpulsatile, predominantly central-type severe disabling subjective idiopathic tinnitus. Waveform categories A-E are defined in the text.

Group 2 Subjects, Sequential Recording	7/07	9/07	10/07	11/07	3/08	8/08	11/08	4/09	3/12
(2.1)	B,D	B,D	A,D	A,C		A,C	B,D		B,D
(2.2)	B,D								A,D
(2.3)	B,D				B,D			B,D	B,D
(2.4)								E	A,C
(2.5)		A,D			A,C			A,D	A,C
(2.6)								A,C	A,D

Figure 4. Tinnitus summary, group 2: Tympanic membrane displacement (TMD) in a cohort of patients with nonpulsatile, predominantly central-type severe disabling subjective idiopathic tinnitus. Waveform categories A - E are defined in the text.

a reduction in the subjective SIT relief reported in March 2012. In retrospect a prognostic marker of increasing SIT intensity, reported in March 2012, was alteration in the TMDT recordings of CC - not IPPA ICP - from August to November 2008 (i.e., a reduction in CC that preceded the increase in ICP recorded in November 2008).

Tinnitus treatment results targeting ICP as a manifestation of IIH with Diamox were positive in the short term (n = 2). The SIT relief is reflective of fluctuation in the ICP and the multifactorial conditions influencing brain pulsatility.

In summary, this case report demonstrates (1) fluctuation of the ICP, which correlated with the clinical subjective report of SIT intensity; (2) the significance of sequential measurements of the TMDT, which reflects the dynamic state of the CSF ICP in a SIT patient and its application for treatment; and (3) the dual function of the TMDT for diagnosis and as a monitor for treatment efficacy.

DISCUSSION

Goals, revisited

In a preselected group of SIT patients (n = 12) resistant to attempts for tinnitus relief with instrumentation or medication, an abnormal ICP has been identified (n

= 10). This preliminary report of the clinical application of the TMDT for identifying an abnormal IPPA ICP in a particular cohort of SIT patients is considered to have accomplished the goals of the project.

1. IPPA ICP with TMDT

Spontaneous recordings of abnormal IPPA ICP were identified with the TMDT in groups 1 and 2 for a preselected SIT population suspected clinically of having an abnormal ICP. The addition of the clinically associated complaints reported by this special cohort of SIT patients into the MATPP may be the basis for a clinical protocol for identifying abnormal ICP and the diagnosis of IIH.

The result of abnormal ICP with reduced compliance (n = 7/12) and normal ICP with reduced compliance (n = 2/12) are considered clinically significant. The concept of compliance (i.e., "elasticity" of the CSF and brain volume in the enclosed cranium) in relation to the ICP, an exponential pressure-volume relationship in the cranium, may have clinical translation for treatment of this particular cohort of SIT patients. Specifically, the concept of compliance and the TMDT results in SIT patients with abnormal ICP and reduced compliance, normal ICP with reduced compliance and, possibly, abnormal ICP with normal compliance may supplement classical clinical thinking about the medical significance of a CNS complaint, to be based not only on the absolute value of the ICP but on the relative value of ICP and compliance, a mathematical approximation based on observed data, for brain disease diagnosis and treatment.

The fluctuations in the categories of the TMD recordings in the same patient at single or sequential recording dates are clinically considered to be a reflection of the dynamic state of the ICP and compliance in the presence of SIT and the influence of the environment and presence or absence of CNS disease. Direct and or indirect measurements of the ICP are considered to be relative, not absolute, values. These claims are supported by a recent article that concluded that the pulsatility of the ICP may be more relevant than static ICP in the diagnostic setting for patients with IIH[38].

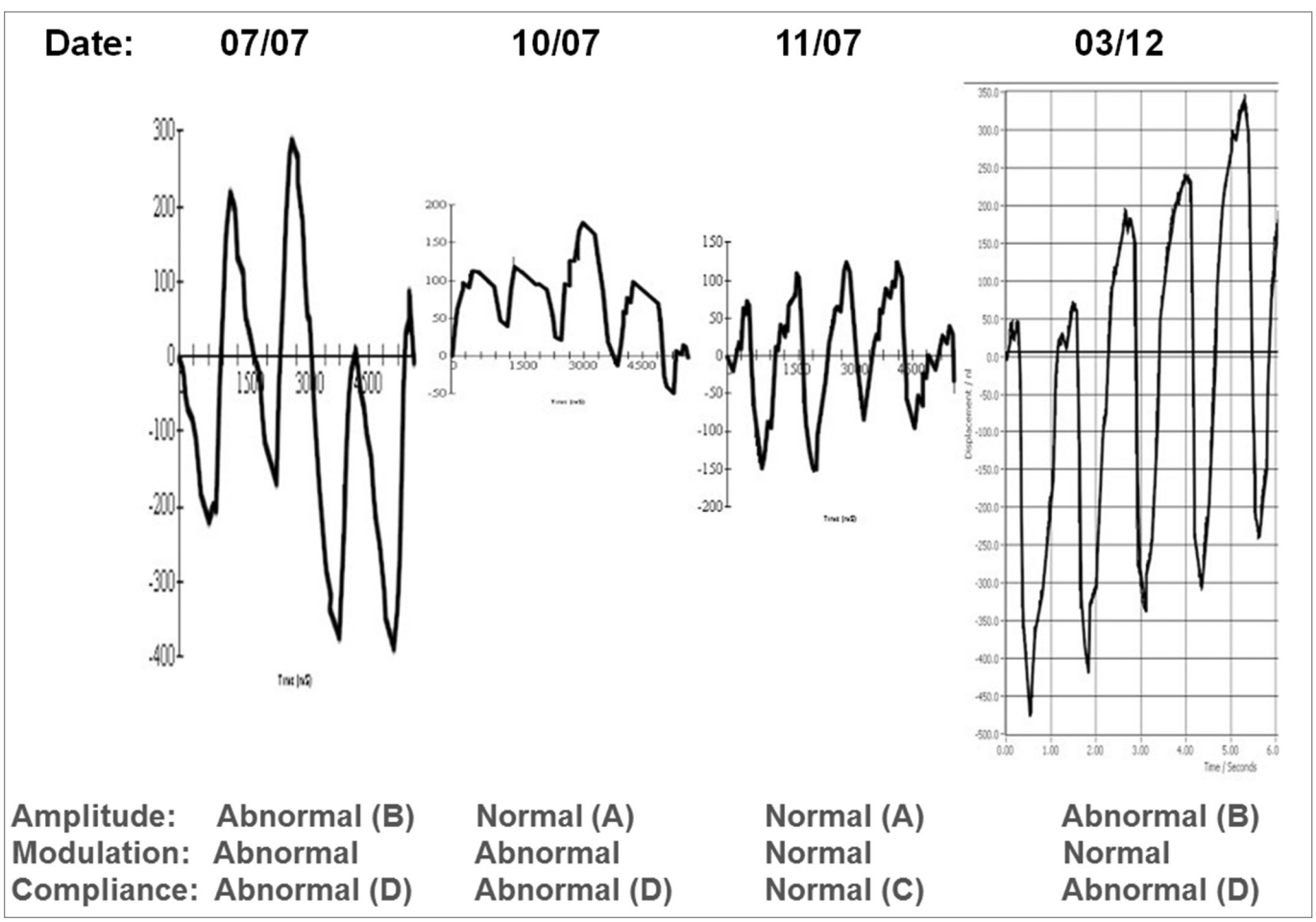

Figure 5. Serial measurements in patient 2.1. Waveform categories A-E are defined in the text. (x axis in milliseconds; y axis in nanoliters).

2. IPPA ICP as a positive indicator for IIH

The results of a normal or abnormal ICP and reduced or normal compliance in this cohort of SIT patients supports clinical consideration of the presence of an IIH and indication for treatment. Both ICP and compliance may be factors influencing the clinical course of SIT in a preselected cohort of affected patients: Identification and treatment of these factors may influence the associated complaints cited previously and also may influence the clinical course in this particular cohort of SIT patients.

3. Tinnitus TMDT, spontaneous (not evoked) test mode

Spontaneous TMD recordings of intra-aural pressure waves were obtained in this cohort of SIT patients. The test-retest reliability of the TMD was positive, as demonstrated by the repeated TMD results recorded in both group 1 and 2 patients (see Figures 3,4). The spontaneous, not the evoked, mode of elicitation of intra-aural pressure waves is recommended for TMD testing in SIT patients, specifically to avoid a potential increase in tinnitus intensity that may accompany the audiological threshold recommended for eliciting the acoustic reflex in the evoked mode of the TMD.

4. TMDT Tinnitus, real-time IPPA ICP diagnosis and treatment

The sequential serial measurements on different TMD recording dates in group 2 supports a dual function of the TMD: first, diagnosis - identification of IIH by abnormal ICP and its fluctuation in the presence IIH, the clinical value of serial rather than single-session recordings of the ICP on a single date being reflective of the dynamic state of the ICP; and second, a monitor function of the TMD for use before and after treatment targeting the ICP (see Figure 4).

5. Tinnitus relief, TMDT ICP IIH treatment monitor function

The serial sequential recordings on TMD testing of abnormal and normal ICP in the case reported in this article (see Figure 5) clinically correlated with the patient's clinical subjective report of fluctuation in SIT intensity and tinnitus relief (i.e., improvement when was ICP normal and increased tinnitus intensity and annoyance with abnormal ICP). The clinical significance to the patient of restoring the ICP from abnormal to normal for tinnitus relief was positive for the interval of TMDT testing reported at this time. However, our clinical experience with SIT is the basis for recommending interval examination, including repeat TMD testing, to establish the clinical significance of ICP identification and treatment for long-term tinnitus relief and the diagnosis of IIH.

The clinical significance of abnormal ICP and IIH as factors influencing the clinical course of SIT is suggested by the TMDT results we have obtained. However, these results are rather limited. Long-term follow-up is recommended in a large specific cohort of SIT patients to establish the incidence of abnormal ICP and IIH and the medical significance of such findings for long-term tinnitus relief.

6. TMDT limitations and complications

The TMDT was found to be a safe, nonsurgical test for its stated indication in this report (i.e., extracranial identification and monitoring of the IPPA ICP and perilymphatic pressures in a particular cohort of preselected SIT patients). No TMDT complications ensued in the SIT population discussed in this article. Nonetheless, limitations include the following:

- The essential requirements of the TMDT are integrity and patency of the external ear canal, an intact tympanic membrane, and an intact ossicular chain. A patent cochlear aqueduct or an alternative intracranial-labyrinthine fluid communication route is required for ICP and compliance assessment. Desirable, although not essential, are normal immittance testing and type A tympanometry reflective of normal aeration of the middle ears; normal acoustic reflex testing; and integrity of the sound conduction-transduction system in both the middle and inner ear.
- The spontaneous TMD is likely to be modified if these factors are found to be abnormal.
- The TMDT is to be performed only in the absence active acute or chronic inflammatory ear disease.
- The normative database for the TMDT is limited. There is a need for an increased number of normal subjects with appropriate demographic data including age and gender.
- TMD testing in tinnitus patients should be performed in the spontaneous, not the evoked, mode of recording to obtain the intra-aural pressure waves.
- Compliance as implied by TMD is reported as an extrapolation of the volume-pressure relationship in brain, not as an absolute value.
- Maintenance of a seal in the external ear canal is important and is considered to reflect the learning curve (i.e., experience) of the tester.

7. Brain pulsatility otology and neurotology

Clinical and basic science efforts at identifying the clinical significance of brain pulsatility have been ongoing for in excess of 60 years[39]. Introduction of the TMD is but one of a number of approaches for external identification of the ICP. Other technologies include transcranial Doppler ultrasonography and phase-contrast MRI. The data obtained have identified different morphologic types of waveforms. Raw-data analysis of the intracranial waveforms has been supplemented by systems analysis, all of which is providing clinical markers of disease in brain and fluid dynamic relationships with eye and ear, thereby improving the accuracy of diagnosis of the complaint and its site of lesion.

This report of using the TMD lends credence to the application of brain pulsatility to support the diagnosis of IIH in a particular cohort of SIT patients. Its clinical translation for tinnitus relief awaits larger clinical trials and outcome determinations that differentiate for SIT between control of the ICP and IIH and patients' report of tinnitus relief.

Idiopathic intracranial hypertension

The term *congestive inner ear* was first introduced in patients with increased ICP secondary to tumors[40]. Auditory function was studied in 25 patients with IIH and supratentorial tumors, the majority of whom had hearing loss. Transmission of CSF to perilymph was hypothesized to be via the cochlear aqueduct and was the etiology of the hearing loss[41]. The initial manifestation of benign intracranial hypertension syndrome as perilymphatic fistula was presented in three cases[40]. An update of this initial experience and its translation for treatment of both perilymphatic fistula and EH was reported in ten cases[43].

Otologic and neurotologic experiences with the TMDT were reported for a series of patients whose diagnoses included pulsating tinnitus, IIH, Ménière's disease, perilymphatic fistula, perilymphatic hypertension, arterial stenosis, and Arnold-Chiari syndrome. The conclusion was that TMDT was a valuable addition to the armamentarium of neurotologists and useful in identifying IIH in cases of pulsating tinnitus[44].

The cohort of SIT patients in this TMD study all had nonpulsatile, predominantly central-type, severe disabling subjective idiopathic tinnitus (SIT) resistant to attempts for tinnitus relief with instrumentation or medication, with associated neurotologic complaints highlighted by ear blockage and sensorineural hearing loss and CNS complaints highlighted by headache, head pressure, and cognitive interference in memory or speech expression or both. IIH is clinically presumed to be present based on the TMD results of abnormality in the spontaneous intra-aural pressure waves (n = 10/12) in this particular cohort of SIT patients.

This cohort of SIT patients differs clinically from the pulsatile tinnitus associated with IIH and identified as benign intracranial hypertension[13,14]; for this cohort, the following features applied:

- SIT was nonpulsatile and predominantly of a central type, with a high-frequency quality, located in the ears or head.
- Associated complaints included ear blockage in the SIT ear, and CNS symptoms of headache, head pressure, and cognitive interference in memory or speech expression or both.
- The ICP was identified not by lumbar puncture but with an externally placed ear canal device.
- The ICP reflecting IIH is presumed to underlie the abnormal spontaneous intra-aural pressure waves identified with the TMDT and is a factor in, not the etiology of, the clinical course of this particular cohort of SIT patients. The etiology of the IIH is presumed to be cerebrovascular arterial hypertensive disease, not venous disease, based on the clinical history of this patient cohort.
- The pathophysiology is incomplete but we hypothesize that the disease features in this cohort reflect fluctuation in IIH, which is in turn reflective of alterations in the intracranial cardiovascular and respiratory wave pulsations.

Ear blockage

The associated complaint of ear blockage or aural fullness is clinically hypothesized to reflect fluctuation in the ICP of a persistent IIH. Transmission of the CSF increased intracranial cardiovascular and respiratory wave pulsations primarily via the cochlear aqueduct affects the perilymphatic compartment of the cochlear labyrinth[24,25]. Intracranial subarachnoid CSF pressure transmission onto the endolymphatic sac results in an initial increased pressure into the endolymphatic duct, which, over time, results in EH and SEH. It is hypothesized that fluctuation in the degree of the abnormal ICP and compartmentalization of the increased pressure effect within the cochlear and vestibular labyrinths of this transmitted pulsation on the underlying sensorineural tissue become clinically manifest in gradually increasing complaints of ear blockage, tinnitus, vertigo, and hearing loss in some SIT patients. This hypothesis is supported by the evidence of animal and human studies previously cited in this article.

Compartmentalization

The concept of compartmentalization, the separation and differential effect of a physical force of one region from another, is considered to be important for understanding the fluid dynamics in and between brain and ear, and its clinical application for measurement of an ICP with an external device (e.g., TMD) and for the clinical translation of this measurement for otologic and neurotologic complaints of hearing loss, tinnitus, ear blockage, and vertigo. Briefly, fluctuation in cardiac output has two effects on intracranial dynamics - temporal changes on pressure and flow. Specifically, pressure pulses are not dependent on location and can be measured anywhere within the cranium, whereas flow pulsations are highly dependent on location of measurement. Pressure measurement is usually restricted to the lateral ventricle, cisternum magnum, or brain parenchyma. Flow measurement varies with magnitude and pulsatility of the flow, the type of fluid, and the location. The TMD measurement of the cardiovascular and respiratory intracranial pulsations is predominantly that of the subarachnoid compartment of the intracranial CSF system[37]. Significant is the compartmentalization already in place in the anatomic distribution of the fluid systems of the inner ear.

Cerebral blood flow autoregulation

Cerebral blood flow autoregulation (CBA) is the process by which cerebral blood flow is maintained at a constant level in normal brain. Cerebral blood flow is determined by multiple factors including blood viscosity, degree of dilatation of blood vessels, and cerebral perfusion pressure. The cerebral blood flow is equal to the cerebral perfusion pressure divided by the cerebrovascular resistance[45]. The serial recordings with the TMD speculatively provide a monitor for recording of CBA (see Figure 4).

Cerebral perfusion pressure is the net pressure gradient causing blood flow to the brain (i.e., perfusion). Increase in blood flow results in an increase in the ICP; decrease results in an ischemia.

The pressure - volume relationship among ICP, volume of CSF, blood, and brain tissue and cerebral perfusion pressure is known as the *Monro-Kellie doctrine* or the *Monro-Kellie hypothesis* (1783). This hypothesis states that the cranial compartment is incompressible, and the volume inside the cranium is a fixed volume. The cranium and its constituents (blood, CSF, and brain tissue) create a state of volume equilibrium, such that any increase in volume of one of the cranial constituents must be compensated by a decrease in volume of another[44].

Brain and ear: relationships among volume, pressure, and compliance

The concept of compliance is the ratio of volume change to pressure change. Clinically, it can be considered to be the elasticity or rigidity of contents, fluid and solid, in a given space. Graphically, the compliance of a system is inverse to the slope of the pressure - volume curve. With an increase in ICP, the concurrent reduction in intracranial compliance results in an increase in the pulse wave amplitude. The measurement of the compliance is not direct but rather indirect extrapolation of the ratio of volume change to pressure change. With increasing pressure, the IPPA increases more than the volume[28].

The issue of compliance has also been reported in experimental findings related to inner ear fluid pressure and to the effects of pressure changes on cochlear function in the guinea pig. A high compliance of Reissner's membrane seems to be the cause of this endolymphatic - perilymphatic pressure equalization. In experimental EH, endolymphatic pressure is higher ($\geq$ 100 Pa) than perilymphatic pressure. These pressure gradients occur only in late stages of hydrops, probably when Reissner's membrane has lost its high compliance after long-standing distension[20].

The concept of compliance and its extrapolation from the ratio of the volume-pressure curve, obtainable with the TMD as a high amplitude of the cardiovascular pulse pressure, is significant for its clinical translation for evaluating the status of homeostatic function in both ear and brain. The significance of CC is demonstrated in the serial recordings of the TMD in the case report (see Figure 5). Specifically, a reduction in CC with a normal IPPA ICP preceded an increase in IPPA ICP and a reported subjective reduction in tinnitus relief. The correlation of the TMD recordings with a focus on the issue of intracranial volume-pressure relationships and compliance (i.e., IPPA ICP and CC) may be a method not only for the early identification and treatment of the factor of IPPA ICP for a particular cohort of SIT patients but also as a monitor function for objective identification of treatment efficacy for this factor and tinnitus relief.

EH, SEH, and IIH

EH is an enlargement of the endolymphatic space with a bulge of Reissner's membrane into the scala vestibuli of the cochlear labyrinth. In our ongoing clinical neurotologic experience for SIT since 1972, and with a focus on SIT since 1979, the occurrence of SEH has been reported to be significant, and this diagnosis has been found to influence the clinical course of SIT and associated complaints of hearing[5,47].

The finding with TMDT of an elevated IPPA in the SIT ear, which supports the diagnosis of IIH in the present cohort of nonpulsatile SIT patients, is the basis of the following questions and hypothesis: Is the SEH that has been clinically identified in some SIT patients since 1981 with the MATPP and that is supported by vestibular testing in some SIT patients with and without vertigo a clinical manifestation of a IIH? Is what is diagnosed as SEH, a particular type of EH, a clinical reflection of increased IPPA and IIH? Is the primary origin and pathophysiology of the otologic histopathophysiologic correlate of EH the brain and not the ear? Is the finding with the TMDT at this time in a preselected cohort of SIT patients of an increased IPPA ICP support for consideration that the IPPA and cardiovascular disease may be an etiology for a subgroup of EH, SEH, and Ménière's disease patients?

We suggest that the volume-pressure relationships in a confined space be applied clinically to the ear as they have been for the brain. Specifically, the primary etiology for a particular type of EH may be cardiovascular and the clinical marker may be the increased IPPA and IIH.

It is hypothesized for some, but not all, EH and SEH patients that the IPPA, reflecting alterations in volume - pressure relationships in brain, is transmitted to the ear predominantly by one or both of two routes - via the cochlear aqueduct or via pressure on the endolymphatic sac. The result via the cochlear aqueduct is an increase in perilymphatic pressure. The result via pressure on the endolymphatic sac influences volume, pressure, and compliance changes in the endolymphatic duct, which, over time, results in extension and distention of Reissner's membrane into the scala vestibuli. The net effect of both routes of IPPA transmission, in ear as in brain, is a reduction in compliance as the pressure within each compartment is increased, with interference in underlying structure and function and clinical manifestations of hearing loss, tinnitus, vertigo, and ear blockage.

The teaching from brain of compartmentalization of the effects of pressure and flow, which, although related physical phenomena, differ in the location for their measurement, are suggested to apply to the ear: That is, pressure pulses propagate at the speed of sound and the location for their measurement are not specific, but flow pulsations are site-specific[39].

The Monro-Kellie hypothesis for brain applies to the ear. This view of pressure - volume alterations in brain, manifested by an increased IPPA and IIH, is considered to be supported by current thinking for hearing loss and Ménière's disease. Specifically, "endolymphatic hydrops may initially not be pathologic, and the symptoms arising from hydrops may be mild or negligible, but … over time there are secondary changes in ion transport systems that result in hearing loss"[48].

"For vertigo associated with EH, an alternative explanation involves endolymph volume changes during the attack, mechanically disturbing semicircular canal hair cells, causing an initial stimulation followed by inhibition. The underlying endolymph volume change may result from a change in transport (such as if the endolymphatic sac switches from secreting fluid to resorbing fluid) so that endolymph volume declines with time without a membrane rupture taking place. In the normal cochlea, the rate of longitudinal endolymph flow is extremely low, so that flow does not make a significant contribution to the homeostasis of ions in endolymph. However, recent studies in our lab suggest that when endolymph volume is disturbed, longitudinal flows may be induced that play a part in the recovery of normal volume. These flows may be directed toward the cochlear apex (when endolymph volume is reduced) or toward the cochlear base (when endolymph volume is increased). The conditions under which flows can be induced and the role they play in volume regulation are presently being studied. A concept has been proposed that a disturbance of the resorption system in the endolymphatic sac would cause a "backing-up and an accumulation of endolymph, resulting in the development of hydrops"[49].

CONCLUSIONS

This is the first known report of the clinical application of inserting an external probe device into the external ear canal (Tympanic Membrane Pressure Analyser [Marchbanks] in a cohort of nonpulsatile, predominantly central-type severe disabling tinnitus patients (SIT) suspected to have an elevated ICP reflective of an associated IIH. A physical force, IPPA ICP, was correlated with the behavioral response to the SIT sensation with the TMDT. This application involved recording and demonstrating with single and serial spontaneous recordings an abnormality of the intra-aural pulse pressure waves and fluctuation in the ICP, supportive for the presumption of IIH.

In two groups of these preselected SIT patients, IPPA was demonstrated to be elevated and abnormal and to fluctuate in the clinical course of the SIT (overall abnormality in 10 of the12 patients). Abnormal IPPA was accompanied by reduced CC in 8 of the12 patients, whereas normal IPPA was accompanied by reduced CC in 2 patients, and results were incomplete for the other 2 patients.

The patient preselection protocol used for identifying an elevated ICP and IIH in a particular cohort of SIT patients and the positive results reported for its identification with the TMDT in 10 of our 12 patients supports the continued use and modification of the TMDT reflective of an evolving clinical experience.

The IPPA is reflective of the ICP and was identified with spontaneous single and serial recordings in 10 of 12 SIT patients with postural testing (supine, 30 degrees, and 45 degrees).

The IPPA abnormality, reflective of an increased ICP, is clinically considered to be a factor - not an etiology - for SIT, and is considered to influence the clinical course of SIT in a particular cohort of patients with a predominantly central-type tinnitus. The clinical significance of these preliminary TMDT results for overall tinnitus treatment is to be established over the long term.

Extracranial identification of an IPPA and ICP with the TMDT in the clinical course of SIT has a dual function: identifying ICP as a factor influencing the tinnitus diagnosis, and objectively monitoring the efficacy of ICP-targeted therapy. The correlation of treatment efficacy for ICP control and reported subjective tinnitus relief is considered to be separate and individual for each SIT patient.

The TMDT results of the identification and association of IIH, IPPA, and ICP in this observational report lends support to the clinical impression of an underlying ICP reflective of IIH and a basis for treatment in SIT patients such as those in our particular cohort.

The principles of brain pulsatility are clinically considered to be applicable to the physiology of the inner ear and otologic and neurotologic complaints of hearing loss, tinnitus, vertigo, and ear blockage.

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