

Menière's disease patients improve specific posturographic parameters following diagnostic intratympanic injection

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ABSTRACT

Purpose: Evaluation of specific computerized posturographic parameters in patients with Menière's disease (MD) following the intratympanic injection of gadolinium, a contrast agent, used in radiological diagnosing.

Materials and methods: We have observed 12 adult patients with unilateral Menière's Disease subjected to inner ear magnetic resonance imaging (MRI) examination after intratympanic gadolinium injection (ITG). The diagnoses have been performed according to the guidelines of the American Academy of otolaryngology. Before and after 24 h the ITG, all patients were subjected to the clinical evaluation and computerized posturography (CP), in 4 conditions depending on open/closed eyes and with/without foam cushion under feet.

Results: After ITG, in the affected ear the MRI confirmed the endolymphatic hydrops revealing a thin or even disappeared perilymphatic space. The statokinesigram showed improvement of stability only with closed eyes on a foam cushion. The CP performed 24 h after the contrast intratympanic injection showed a significant reduction of Path Length and Confidence Ellipse Area, due to an improvement of vestibular function on static balance. This improvement could be directly dependent to intratympanic pressure modification mediated by volume of contrast liquid, by "columella effect".

Conclusions: This study demonstrates the absence of vestibular damage in patients undergoing intratympanic gadolinium infiltration and confirms the relationship between intratympanic pressure and vestibular stability modifications providing positive evidences for an applicative use of CP as a functional assessment to better address diagnosis and follow-up in MD patients treated with intratympanic injections..

1. Introduction

Menière's disease (MD) is an idiopathic disorder of the inner ear, characterized by fluctuating hearing loss, tinnitus, fullness and recurrent episodes of rotatory vertigo [[1]].

Today, this pathology remains a complicate pathology to deal with. Since the studies by Hallpike and Cairns [2] and Rauch and others [3], the typical anatomical sign of MD is the endolymphatic hydrops (EH), present also in some asymptomatic patients. Many crucial factors have been proposed in its development such as ionic alterations, gene mutations, autonomic imbalance, autoimmune reactions, viral infections, vascular and allergic alterations, phlogosis and trauma [4–6]. All causes seem to trigger endolymphatic hypertension through different mechanisms that can range from endolymph over-production to re-

duced absorption by the endolymphatic sac, or mechanical obstruction to outflow. For this considerable number of factors, the MD diagnosis is frequently used to describe the symptomatologic triad and from time to time attributed to hypothetical etiological factors. Diagnosis is determined according to the 2015 guidelines proposed by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) with the support of the Barany Society [7].

Due to the impossibility to directly see the hydrops, and the absence of standard instrumental tests or specific clinical signs, clinicians have experienced for a long time a lack of tools for an established diagnosis.

In 2007 a group directed by Nakashima [8] revealed for the first time the presence of hydrops using the MRI 3 T in patients suffering from MD. They demonstrated that the gadolinium (Gd), injected into the middle ear, was carried in the internal ear spreading only in peri-

Abbreviations: MD, Menière's disease; Gd, gadolinium; EH, endolymphatic hydrops; MRI, magnetic resonance imaging; CP, computerized posturography; ITG, intratympanic gadolinium injection; PL, Path Length; CEA, Confidence Ellipse Area; RI, Romberg Index.

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lymphatic spaces, first in the scala tympani of the basal turn of the cochlea and in the vestibule, and the day after it appeared in almost all part of the labyrinth [9]. The spreading of the contrast agent was also reported in other studies. Once more, Nakashima and colleagues reported that the EH appeared as the contrast-absent area surrounded by contrast agents that disappeared about six days after the injection [10]. Moreover, they described the results from MRI scans performed 4 h after Gd injection, reporting a lowering of Gd concentration during the time [11]. In addition, the same authors showed that the intratympanic injection was more effective than intravenous one [12]. Liu and colleagues [13] reported a less invasive intratympanic injection of Gd through the Eustachian tube, also this method made possible to view the EH in patients with MD. All these pieces of evidence support that these methods are free of side effects in the short and long term [9,11–14]. However, comprehensive knowledge about the side effects needs to be enforced. Indeed, until now adverse reactions have not been reported in humans [14], although in animals effects in the inner ear were shown after Gd administration. Tanaka and Colleagues [15] reported alterations in vestibular hair cells from animals subjected to (gadodiamide) administration depending on the dilution of contrast agents.

The hydroptic alterations on physiological functions can be assessed in a more analytical way using the computerized static posturography (CP, i.e. stabilometry throughout the present work) to test the upright stance posture [16,17]. To be specific, MD patients show poor upright posture stability, greatly dependent on visual and somatosensory information [18].

CP represents a non-invasive and effective tool in evaluating the static balance of the patient's body with changes in the vestibular function. This method detects the reflex of the spinal vestibule by recording and analyzing the oscillations and can identify deficiencies in the integration of visual, vestibular and proprioceptive afferents by exposing the patient to various sensory situations [19]. Particularly in MD patients, who have spontaneous vertigo attacks, CP allows evaluating with altered patterns of sensory interaction upon the balance control in the erect position.

Thus, since in the literature no functional alterations related to the intratympanic administration of Gd contrast agent (gadobutrol solution) are described, we aimed to assess whether among MD patients subjected to the injection there were changes in specific posturographic parameters.

2. Materials and methods

2.1. Study design and participants' characteristics

This retrospective clinical study was conducted in our ENT Department of Chieti-Pescara University Hospital on the patients suspected to MD and that were subjected to MRI 3 T with a trans-tympanic injection of gadodiamide. The study protocol was approved by the local ethics committee. All patients provided their written informed consent.

Among all the patients subjected to MRI, 12 adult patients, seven women and five men, aged 38-to-73 years, with unilateral MD were studied. Diagnosis of definitive MD was based on the history of the disease and findings of neuro-otological examinations, which assessed the coexistence of recurrent episodic vertigo and fluctuating cochlear symptoms including hearing loss, tinnitus and aural pressure, according to the 2015 guidelines proposed by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) with the support of the Barany Society [7]. All patients underwent audiological and otoneurologic examinations, to exclude other inner-ear disorders and retro labyrinthine disorders. Exclusion criteria were previous otologic surgery, ablative therapy with gentamicin, patients with superior canal dehiscence syndrome (SCDS) or enlarged vestibular aqueduct syndrome (EVAS) or any other temporal bone abnormalities. Subjects with a his-

tory of inflammatory middle ear disease and those patients that cannot undergo MRI were also excluded; none of the patients was in an acute ear phase, no one had ever utilized the Meniett device nor had tympanic perforations nor underwent transtympanic drainage with a drain tube insertion.

2.2. Intratympanic gadolinium injection (ITG) and magnetic resonance imaging (MRI)

The injection was performed in the affected ear after administration of local anesthetic applied in the external ear conduct. The patient was lying in a supine position with the head turned 30° to the healthy side, so 0.4–0.5 mL of the solution was injected through the tympanic membrane by a 23-gauge needle, using a puncture in the postero-inferior quadrant. The contrast agent was used in the Gadobutrol form (Gadovist - GD) diluted 7-fold in saline solution. After the ITG the patient remained 30 min with the head turned 45° to the healthy side to permit the diffusion through the round window. 3 Tesla MRI was executed before and 24 h after the injection, with the acquisition of 3D FLAIR and 3D T2 SE sequences. Multi Planar Reconstructed (MPR) images were analyzed. Vestibular endolymphatic hydrops was graded considering the ratio of the area of the endolymphatic space to the vestibular fluid space (sum of the endolymphatic space and perilymphatic space) [9]. Patients with no hydrops had a ratio of one third or less, those with mild hydrops had between one-third and a half and those with severe hydrops had a ratio of >50%. Cochlear and semicircular canals endolymphatic hydrops were defined positive when an MRI signal void was detected.

2.3. Computerized static posturography (CP)

Subjects were instructed to stand with their feet 7 cm apart and the arms along the sides on a static balance platform for each test sequence. The CP was performed before and 24 h after the Gd injection. The center of pressure between both feet was measured with a computerized vertical force platform (Phisionorm NBP Computerized Posturographic System). Measurements were performed while the subject maintained a 51.2-s upright stance position with open or closed eyes, with or without the presence of a foam cushion under feet. To be specific, during the open eyes conditions, subjects were looking at a small eye-level target 1 m away; the foam cushion was a 100 mm-thick foam rubber mat, exactly with the same size of the balance platform, posed on top of it. Closed eyes condition limited the role of vision control of upright stance, while foam cushion conditions limited the somatosensory and proprioceptive information [20]. Each test was conducted under visually and acoustically standardized conditions, in a room with white walls and uniform brightness. Each test was followed by a 30-s interval. The parameters considered before and after the intratympanic injection were: Path Length (PL), defined as the linear length (mm) of the sway path; Confidence Ellipse Area (CEA), defined as the area of the 95% confidence ellipse around the Center of Pressure (CoP) trajectory [21]. We focused on these parameters because of their large use and validity in double-stance static balance assessment [21]. We then calculated Romberg Index (RI), as the percentage ratio between the value of PL, or CEA, with closed eyes and the same parameter obtained with open eyes.

2.4. Statistics

The statistical analyses were carried out using GraphPad Prism Software, version 7 (GraphPad Software, La Jolla, USA), and R-based open-source software Jamovi (The jamovi project 2019 – jamovi, (Version 0.9) [Computer software]) and Jasp (JASP Team (2019). JASP (Version 0.11.1) [Computer software]). The identification of outliers was per-

formed with the ROUT method ($Q = 0.5\%$). The normality of the distributions was assessed with the Shapiro-Wilk test and checking Q-Q plots of residuals. After acceptance of normality assumption checks, we used paired t -test to analyze the pre-post differences. For each comparison, we considered p values and Effect Size (Cohen's d) and calculated 95% Confidence Intervals (CIs) of mean differences. In addition, we calculated the probability of superiority (PS), as the percentage of a randomly sampled member of the higher mean distribution having a higher score than a randomly sampled member of the other distribution, and unbiased Cohen's d , to adjust for a likely overestimation of effect size due to the small sample size [22]. We complemented the frequentist approach with the Bayesian approach to provide additional information for hypothesis testing [23]; in particular, we used Cauchy's prior distribution, reported Bayes Factor (BF_{10}) and performed robustness check. Our approach permitted us to rate the various comparisons, and consequently to identify the posturographic parameters and test conditions most responsive to the injection.

3. Results

No adverse reactions and no audiological or vestibular complications and no damage to the eardrum membrane, as persistence of perforation, were observed after Gd injection in all the 12 patients recruited for this study. The MRI indicated the presence of hydrops in 10 patients while in the remaining two cases the exam was negative. In particular, the MRI performed with the contrast medium, indicated the diffusion of Gd in the structures of the inner ear only in those 10 patients bearing the hydrops. The possibility of not observing the diffusion of the contrast medium has already been reported [24]. In all cases the clinical signs of hydrops were present, indeed, the remaining two patients that did not present the diffusion of the contrast agent reported to have suffered from otitis in childhood. The otitis may indeed have altered the anatomy of the district, hindering in MRI examination the diffusion of Gd in perilymphatic space.

Data of PL and CEA are shown in Figs. 1 and 2, respectively, and Table 1 collected the results of statistical analyses of these parameters. The most relevant difference was found for PL in eyes closed plus foam cushion under feet condition, with a significant reduction 24 h-after injection ($p = 0.011$, Cohen's $d = 0.876$, $BF_{10} = 5.328$). Robustness check of Bayesian statistics showed that the evidence was moderate and robust, close to the max BF_{10} (5.330) and relatively stable across a

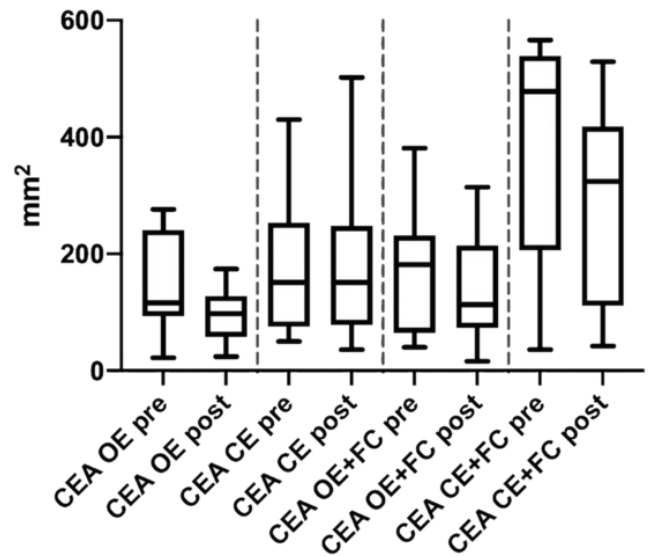


Fig. 2. Confidence Ellipse Area (CEA) of MD patients before (pre) and 24 h-after (post) the intratympanic injection; OE: Open Eyes; CE: Closed Eyes; FC: foam cushion under feet. Data are presented as boxes and whiskers (with Tukey method).

Table 1

Statistical comparison between stabilometric parameters: Path Length or Confidence Ellipse Area, measured pre and 24 h-post intratympanic injection on MD patients. In the table are reported the Eye condition (Eye), the presence of foam cushion under feet (FC), the statistical significance (p , $*p < 0.05$), the Effect size (Cohen's d) and the Bayes Factor (BF_{10}).

	Eyes	FC	p	Cohen's d	BF_{10}
Path Length (PL)	Open	No	0.199	0.394	0.610
	Open	Yes	0.668	0.127	0.313
	Closed	No	0.443	0.230	0.376
	Closed	Yes	0.011*	0.876	5.328
Confidence Ellipse Area (CEA)	Open	No	0.145	0.453	0.759
	Open	Yes	0.877	0.046	0.291
	Closed	No	0.884	0.043	0.290
	Closed	Yes	0.046*	0.688	1.832

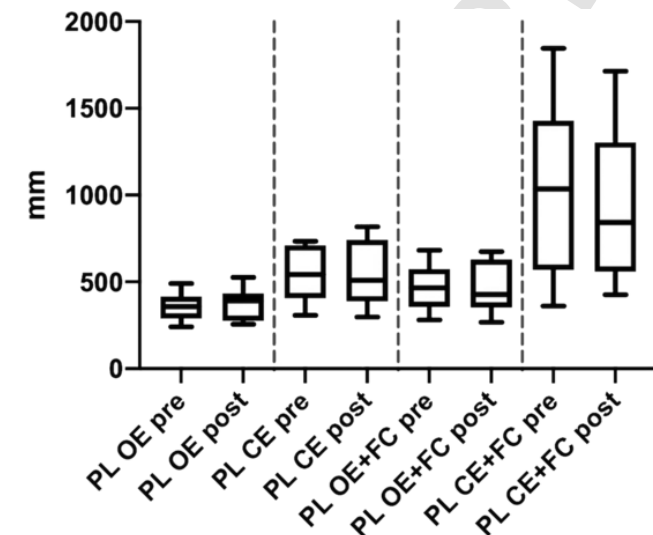


Fig. 1. Path Length (PL) of MD patients before (pre) and 24 h-after (post) the intratympanic injection; OE: Open Eyes; CE: Closed Eyes; FC: foam cushion under feet. Data are presented as boxes and whiskers (with Tukey method).

wide range of prior distributions. Unbiased Cohen's d was calculated as 0.815; PS was calculated as 71%. CI of mean difference was in the range of 31-to-200 mm.

A similar result was obtained analyzing CEA data resulting in a significant decrease in eyes closed plus foam cushion under feet condition ($p = 0.046$, Cohen's $d = 0.688$, $BF_{10} = 1.832$). Robustness check showed that the evidence was smaller in respect to the above-mentioned PL comparison, but robust (max $BF_{10} = 1.938$, relatively stable across a wide range of prior distributions). Unbiased Cohen's d was calculated as 0.640; PS was calculated as 67%. CI of mean difference was in the range of 2-to-176 mm².

Concerning RI of PL, there was a significant reduction 24 h-after injection (2.15 pre vs 1.97 post) in foam cushion condition, while there was no difference without foam cushion (1.52 pre vs 1.50 post) (see statistical analysis in Table 2). RI of CEA appeared to be decreased 24 h-after injection in foam cushion condition (3.73 pre vs 2.78 post) and appeared to be increased without foam cushion (1.09 pre vs 1.73 post), although the statistics did not provide robust evidence (see statistical analysis in Table 2). As well as the above-mentioned statistics of CEA, for RI comparisons robustness checks highlighted robust but weak differences.

Table 2

Statistical comparison between stabilometric parameters: Romberg Index of Path Length or Romberg Index of Confidence Ellipse Area, measured pre and 24 h-post intratympanic injection on MD patients. In the table are reported the presence of foam cushion under feet (FC), the statistical significance (p , $*p < 0.05$), the Effect size (Cohen's d) and the Bayes Factor (BF_{10}).

	FC	p	Cohen's d	BF_{10}
Romberg Index of PL	No	0.675	0.125	0.312
	Yes	0.046*	0.648	1.762
Romberg Index of CEA	No	0.055	0.654	1.585
	Yes	0.077	0.562	1.193

4. Discussion

The MRI with intratympanic injection of the contrast agent is the sole method currently applicable to observe directly the EH in living patients with MD. Once released into the tympanic cavity the Gd goes through the round window into perilymphatic space of the vestibule, and then within 24 h to the cochlea and the semicircular canals. The 3 T MRI with ITG allowed us to correlate MD signs and symptoms [25] and monitor the effects of pharmacological treatments for hydrops.

Firstly, CP is used to evaluate patients with balance alterations: this technique allows not only quantification of the subject's capacity to maintain an upright stance posture, but also allows the analysis of the impact of various sensory information.

Furthermore, it is well known that MD patients are sensitive to low-frequency sounds, probably due to the activation of vestibulo-spinal responses. These responses seem to be the result of the Tullio phenomenon in which sound energy activates the vestibular end-organ [26]. In this regard, CP protocols indicated a significant relationship between the audiometric hearing threshold and the center of pressure displacement, especially in patients with audiometric advanced disease [27]. In addition, posturography tests are sensitive to the time elapsed since the last typical vertigo attacks [28].

Considering the frequent poor stability in the upright posture of MD patients [18], we aimed to verify if the injection of contrast agent solution in the tympanic cavity could affect patients' stability, measured by static CP. Therefore, the CP tests were performed in diverse conditions: open and closed eyes and with or without foam cushion. The lack of visual support (closed eyes) and the reduced proprioceptive feedback (presence of foam cushion) produced a stabilometric result mainly led by the vestibular system.

Our results demonstrated a reduction of PL and CEA in closed eyes plus foam cushion condition, 24 h-after the injection, indicating a postural stability improvement in respect to the identical condition before the injection. This suggests that this improvement could be led by the vestibular system.

Some authors found a visual dependency pattern in patients with vestibular dysfunction [29–31]. In our study, the Romberg Index decreased after the injection in foam cushion condition, both in PL and CEA, suggesting that the vestibular more notable control after the injection may reduce the impairment due to the lack of visual control and proprioceptive feedback.

The intratympanic injection was followed by a period of at least 30 min. During this time, patients must remain in a position that ensures the maintenance of the contrast medium between the tympanum and the round window. This procedure may lead to the following consequences; the first one is tympanum perforation, which inevitably modifies the pressure ratio between the external auditory canal and the tympanic cavity. The pressure ratio is high enough to imply an accessory perforation in the epitympanum, to prevent an excessive increase of pressure during the infiltration. If an epitympanic perforation is un-

performed, as on our subjects, the insertion of the Gd solution can rapidly increase the pressure in the tympanic cavity. This pressure, as reported by Feijen [32], is transmitted directly into the structures of the inner ear; because in MD patients the symptomatology can be mediated by pressure alteration [33], this effect could modify vestibular hair cells function. A further consideration concerning the contrast liquid inserted into the tympanic cavity is that the injection creates a direct connection between the eardrum and the round window; this effect is known as the "columella effect", i.e. any sound produced in the environment is transmitted directly to the round window and then in the inner ear distributing sound pressure into perilymphatic spaces [34]. This modification of perilymphatic pressure, as well as endolymphatic one, can modulate cochlear and vestibular hair cells function; this function, through vestibulo-spinal responses, entails to postural changes [26].

In addition, the conditions generated by ITG are similar to the ones generated by the Meniett device in the treatment of MD [35] without tympanostomy. This device delivers intermittent low-pressure pulses through a tympanostomy tube (grommet) to the middle ear space, then acting on the round window membrane. Since the fluids of the inner ear are incompressible, the energy of the pressure pulses causes a displacement of the perilymphatic fluid. This stimulates endolymphatic fluid flow, resulting in a reduction of static endolymphatic fluid. The same functional complications (i.e. tinnitus increase in 5.4% of patients, transient dizziness in 16.9% and vertigo in 1.8% of subjects) were obtained after transtympanic injections, as a consequence of the modification of intratympanic and intralabyrinthine pressure [36]. We therefore planned to carry out CP tests before and 24 h-after ITG to study vestibular stability.

A similar approach, measuring serial posture oscillation and center of pressure displacement and area, was used by Narita et al. [37] who followed up 31 patients with vestibular dysfunction for a period of approximately 260 days. They found a correlation of clinical improvement and reduction of posture oscillations with time, confirming the usefulness of the test to follow up patients with vestibular dysfunction. From our results, we conclude that the increased stability after the intratympanic injection was predominantly due to a vestibular function improvement.

The CP parameters measured in this study, PL and CEA, are scientifically appreciated [21] and we support their use as functional measures in MD patients. These parameters allow discriminating the impact of the vestibular function on upright stance postural control. Romberg Indexes need to be better evaluated in larger samples, to better clarify the eventual role of such indexes in the evaluation of MD patients. PL, rather than CEA, seemed to better adhere to the rationale of postural control in MD patients. Statistics revealed PL in closed eyes plus foam condition as the most adequate functional measurement in evaluating static postural affection in the current study, with moderate and robust evidence [22,23]. Further studies should address the role of Load Distribution Difference parameter in the evaluation of MD patients, relating it to the side of the disease.

Recently, Wesseler and colleagues reinforced the diagnostic value of MRI performed 24 h after intratympanic Gd injection in MD: they demonstrated this procedure to be the most reliable to diagnose MD, in respect to other functional tests; indeed, none of those diagnostic vestibular functional procedures served as an indicator of endolymphatic hydrops [38]. With the current work, we extended this evidence in a functional basis, revealing how injection affected static balance where a vestibular impairment emerged.

Further studies may also discriminate between the specific Gd injection and a control injection, to test the effect of fluid volume and specific substances commonly used in MD analyses. Plus, further studies may investigate the effect of intratympanic injection in control vs MD patients.

5. Conclusions

The intratympanic injection of contrast solution in the middle ear of MD patients improved some specific posturographic parameters 24 h after the injection. In particular, we demonstrated a significant improvement of the vestibular function with eyes closed on a foam cushion under feet. We think this improvement is causally related to the intratympanic pressure modification mediated by the volume of contrast liquid, by means of the “columella effect”. This study confirms the relations between intratympanic pressure and vestibular stability modifications that can be also subclinical. CP parameters could be measured, in longitudinal studies or pharmacological intervention, to monitor MD patients and to discriminate the vestibular component on the postural control.

CRedit author statement

Conceptualization: GN, AS, MAM.

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Investigation: GN, AS, AT, LN, FC.

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Writing - Review & Editing: GN, DB, AS, AT, LN, FC, NP, MAM.

Visualization: DB, NP.

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Declaration of competing interest

The authors have no competing interest to declare.

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