Prevention of Otitis Media With Effusion by Repeated Air Inflation in a Monkey Model

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Objectives: To test the following hypotheses that (1) middle ear (ME) air inflation prevents the development of otitis media with effusion in a monkey model of functional eustachian tube obstruction, and (2) ME inflation treatment of otitis media with effusion can cause artifactual clinical improvements due to fluid displacement from the tympanum to the adjacent airspaces.

Design: Randomized controlled trial.

Subjects: Twelve cynomolgus monkeys.

Interventions: Eustachian tube dysfunction was induced by botulinum paralysis of the right tensor veli palatini muscle in all monkeys. Before and on study days 9, 15, and 21 after paralysis, the presence or absence, and distribution of ME effusion were documented using magnetic resonance imaging (MRI). Right and left ears were examined twice daily for 21 days using tympanometry, and right ME air inflation (n = 6 ears) or sham inflation (n = 6 ears) was done immediately after those examinations if the ME pressure was −100 mm H2O or less. On 10 of the scheduled MRI evaluations, the MRI was repeated immediately after an inflation to document the possible redistribution of fluid within the ME caused by the maneuver.

Results: Middle ear pressure remained within normal limits for the follow-up period in 11 of the 12 nonparalyzed left ears, in none of the 6 sham-inflated right ears, and in 3 of the 6 air-inflated right ears. Three air-inflated right ears developed flat tympanograms (ie, days 14 through 16). Magnetic resonance imaging documented inflammation and fluid in 1 of the 11 nonparalyzed left ears and in all sham-inflated right ears. Lesser degrees of inflammation and effusion based on MRI evaluations were noted for the 3 air-inflated right ears that retained near-ambient pressures when compared with the right 3 ears that developed a flat tympanogram. The MRI measure of effusion quantity within the tympanum was decreased acutely after inflation, but was simultaneously increased in the adjacent airspaces of the temporal bone.

Conclusions: Repeated air inflation prevented the development of otitis media with effusion in 50% of the ears with functional eustachian tube obstruction. Postinflation MRI documented the displacement of fluid by inflation from the tympanum to the mastoid and petrous air cells. Using standard clinical evaluations such as tympanometry and otoscopy, this fluid redistribution can cause a false diagnosis of improvement.


Otitis media with effusion (OME) remains a treatment challenge. Concerns regarding the long-term complications and sequelae of both the disease and the current treatment methods have renewed an interest in middle ear (ME) inflation as a treatment option. While the efficacy of repeated ME inflation for OME is still being debated, anecdotal reports, clinical reviews, and some controlled clinical trials have presented good results. However, for many of those studies, the clinical improvement was followed by relapse on discontinuing treatment.

A recent study convincingly demonstrated that daily ME inflation with the inert gas, argon, did not prevent the development of inflammation and effusion in a monkey model of OME caused by functional eustachian tube (ET) obstruction. There, the presence and persistence of disease was demonstrated using magnetic resonance imaging (MRI), despite in some cases tympanometric evidence of near-ambient ME pressures and near-normal tympanic membrane mobility. Because theoretical considerations suggest that the efficacy of inflation is highly dependent on the timing and frequency of the treatments, the current experiment was done using an identical model system but included earlier treatment onset and more frequent inflation. The primary hypothesis tested was that twice daily ME air-
MATERIAL AND METHODS

STUDY DESIGN

Twelve juvenile cynomolgus monkeys (Macaca fascicularis), weighing between 4.4 and 7.2 kg, were matched for weight and randomly assigned to control (n = 6) or experimental groups (n = 6). Baseline otomicroscopy, tympanometry, and MRI studies were performed, and the right tensor veli palatini muscle of all animals was paralyzed by injection of botulinum toxin. Twice daily for 21 days, animals were examined using tympanometry and, at the first observation of a ME pressure of −100 mm H2O or less and on all subsequent observations, the right ears of animals in the experimental group were inflated via the nose and ET with air. Right MEs of animals in the control group were sham inflated on all days. On days 9, 15, and 21 MRI was performed on all animals. At 10 of those sessions where a ME pressure of −100 mm H2O or less and a postinflation pressure increase were documented, the MRI was repeated after the inflation. The protocol for this study was approved by the Animal Research and Care Committee at the Children's Hospital of Pittsburgh, Pittsburgh, Pa.

SPECIFIC METHODS

For the botulinum toxin injection and the MRI sessions the monkeys were anesthetized with a mixture of ketamine hydrochloride (50 mg/kg), xylazine hydrochloride (15 mg/kg), and acepromazine maleate (2.5 mg/kg). Botulinum toxin (5 U/kg of botulinum toxin type A; Sigma Chemical Co, St Louis, Mo) in a volume of 0.1 to 0.2 mL was injected into the right tensor veli palatini muscle to induce functional ET obstruction and, as a control, the left muscle was injected with 0.1 to 0.2 mL of a saline solution as previously described.7

Twice daily, all monkeys were sedated (intramuscular injection of ketamine hydrochloride, 10 mg/kg) and tympanometry (model GSI 33, Grasen Stadler Middle Ear Analyzer; Grasen Stadler, Melford, NH) was performed bilaterally. Then, air or sham inflation was done if the right ME pressure was −100 mm H2O or less. For air inflation, a small Politzer bag was introduced into the right side of the nose, the velum was elevated digitally, and the bag was deflated quickly. The resulting increased nasopharyngeal pressure caused a passive opening of the ET and transferred a nasopharyngeal air pressure to the nasal cavity and ME.6,8,9 The success of the inflation was documented as an increase in ME pressure on repeated tympanograms. If the right ME pressure was −100 mm H2O or less, inflation as per group assignment was done following the MRI. If the postinflation ME pressure was increased, repeated tympanograms were done at 5-minute intervals, and then the MRI protocol was repeated.

DATA ANALYSIS

The primary data for statistical analysis were the daily tympanometric values of ME pressure and compliance, and the areas of involvement and signal intensities for the MRI studies on days 1, 9, 15, and 21. In calculating the average ME pressure, flat tympanograms were assigned a value of −600 mm H2O. Using the resident scanner software (GE Signa Horizon 5.8; General Electric, Milwaukee, Wis) and previously described methods, T2-weighted MRI images were analyzed for both extent of effusion within the air spaces of the temporal bone (area of involvement) and effusion quantity within the ME proper (signal intensity).7,10–14 Briefly, for each experiment an axial image that included the maximum area of the pneumatized temporal bone and a coronal image that included the maximum area of cochlea were selected.8,9 Two 40-mm2 circular areas over the mastoid and petrous portions of the temporal bone in the axial image, and a 20-mm2 rectangular area over the ME in the coronal image were defined. Signal intensity values for all regions were calculated and then normalized as their ratio to the concurrent value of a reference solution. The mean and SD of the intensity values for those 3 regions were calculated using the resident scanner software. All values are expressed as mean ± SD. Area of involvement was defined as the regional area where the signal intensity exceeded a specified threshold that past studies showed to be indicative of inflammation and/or free fluid.

These MRI data were compared between the right and left ears of all study animals and between the right ears of animals in the control and experimental groups. Second, descriptive analyses were done to compare the responses of the experimental and control right ears for the rate of development of negative ME pressure, the time to achieve ME pressures of −100 or less, −200, and −300 mm H2O, and the time to first observation of a flat tympanogram. Within the experimental group the ears that did or did not respond to treatment were identified and compared for possible contributing factors. Finally, the results of the tympanometric and MRI assessments of ME status were compared for congruence.

RESULTS

Botulinum-induced paralysis of the right tensor veli palatini muscle was confirmed in all animals by the early development of right ME underpressure. Figure 1, A shows the average ME pressures for the right and left ears in inflation, begun at the first observation of underpressure would prevent OME in monkeys with functional ET obstruction. A secondary hypothesis was that a tympanometric diagnosis of an effusion-free ME during the course of inflation treatment is unreliable due to the potential for forced displacement of fluid from the tympanum into the mastoid air cells.
Over the study period, ME pressure remained within normal limits for 11 of the 12 nonparalyzed, left MEs. One left ME of an animal in the air-inflation group developed positive ME pressure by day 3, which was followed by active drainage. Because tympanometry was not performed on the days of drainage, complete tympanometric results for this ear were unavailable.

Right ME pressure of the animals in the control group decreased to −100, −200, and −300 mm H₂O by an average of 1.7 ± 0.5, 4.2 ± 0.9, and 8.5 ± 1.9 days, respectively. Only 1 ear in the control group developed a flat tympanogram by day 21. Middle ear pressure of the right ears in the experimental group decreased to −100 mm H₂O or less by 1.6 ± 0.7 days. These 6 MEs were inflated an average of 19.7 ± 4.2 times.

In both groups, the average signal intensity for the left MEs was essentially unchanged over time (Figure 1, B). While a slightly higher average signal intensity characterized the left MEs of the experimental group, this was attributable solely to the 1 left ME that developed drainage before day 9. The average signal intensity of the right MEs of both groups demonstrated a progressive increase over the 3-week follow-up period.

A post hoc regrouping of the right ears in the experimental group was made based on the response to treatment. Three of these right ears maintained a ME pressure greater than −200 mm H₂O throughout the 21 days of follow-up (Figure 2, A), while 3 right MEs developed flat tympanograms (days 14 through 16) despite repeated inflation (Table). There was a clear difference between the MRI changes for experimental right MEs that did and did not maintain pressures greater than −200 mm H₂O. Specifically, the signal intensity for the 3 ears that maintained pressure was, like the left MEs, relatively unchanged over time. In contrast, the 3 right experimental MEs that developed flat tympanograms had signal intensity vs time functions similar to those for the right MEs of animals in the control group (Figure 2, B). These data are interpretable as documenting the development of ME effusion and inflammation in all 6 right ears (100%) of animals in the control group and in 3 right ears (50%) of animals in the experimental group.

On days 9, 15, and 21, paired preinflation and postinflation MRIs were obtained on 2, 5, and 3 animals, respectively. The average preinflation ME pressure was −300.6 ± 34.2 mm H₂O in 8 of these ears (flat in 2 ears). The average postinflation ME pressure was 143 ± 93.2 mm H₂O with an average time between the 2 scans of 42.3 ± 3.3 minutes. After inflation, the average ME signal intensity decreased from 136.2 ± 98.8 to 92.8 ± 54.4 U (P < .05, t test, 1-tailed) and the average ME area of involvement decreased from 6.8 ± 3.8 mm² to 4.4 ± 4.3 mm² (P < .05, t test, 1-tailed). However, a slight increase was observed in the average signal intensity and area of involvement for the mastoid and petrous portions of the temporal bone, from 217.3 ± 184.1 U and 38.7 ± 31.4 mm² before inflation to 227.8 ± 200.4 U and 39.9 ± 34.2 mm².
after the inflation, respectively. These data support a postinflation redistribution of effusion from the tympanum to the associated air cells. This redistribution can be appreciated visually by comparing the relative brightness of the ME and surrounding regions in the axial and coronal images of the temporal bone shown in Figure 3 for 1 animal with paired preinflation and postinflation MRIs.

**COMMENT**

The 3-century-old idea of Valsalva to aerate the ME by forcing air through the ET was instrumented early in this century by Politzer as a manually compressible air-reserve with an environmental communication that could be sealed within the nasal cavity (Politzer bag). Collapse of the bag during a maneuver that closed the velopharyngeal port increases nasopharyngeal pressure and promotes air exchange across a passively opened ET. In 1962, Gottschalk added concurrent pneumotoscopy to monitor the success of the inflation and to promote, by its pumping action, drainage of effusion down the ET. For cases of serous otitis media (OM), he reported an 81.5% success rate for fluid resolution. However, that method was not easily adapted to the pediatric population in which OME is most prevalent, and alternative, more practical devices and/or methods were developed. For example, Shea suggested swelling water to facilitate ET opening at lesser nasopharyngeal pressures. Hunt-Williams used a carnival blower to assist children with ME inflation and monitored both the achieved nasopharyngeal pressure using a manometer and the desired effect of an ET opening using an otoscope. He reported that while catarrhal cases responded quickly to treatment, secretory otitis required prolonged treatment and/or inclusion of a balloon attached to the device that allowed the child to achieve higher intranasal pressures. Misurya suggested squeezing the inflated cheeks during the late phase of a swallow as a physiologic method of inflation and Bylander et al described a method that included blowing into a mouth-to-nose tube, but reported that 29% of children could not inflate their MEs using the device. More recently, Stangerup et al used a balloon mounted to a nose tube, the Otovent device, and reported a 64% improvement for up to 2 weeks in a clinical trial of children with secretory OM. Blanshard et al reported that the device was associated with tympanometric improvement at 1 month and otoscopic improvement at 1 and 2 months. In controlled clinical trials, Fraser et al and Chan and Bluestone could not demonstrate efficacy of their respective inflation methods for resolution of OME, and both Schwartz and Gimsing reported the rapid return to significant negative pressures after a single, successful inflation.

Despite this lengthy history, inflation remains an unproven method for preventing or treating OME. This may reflect the wide differences among previous efficacy trials for (1) instruments and techniques used for ME inflation, (2) the protocol for initiating and repeating treatments, (3) the characteristics of the study population, and (4) the limitations of the different methods used to monitor ME status. Accepting a role for ET dysfunction in initiating and/or sustaining OME, ME inflation would seem to be a reasonable primary or adjunctive treatment strategy. Hypothetically, introducing gas into the ME by passively forcing the ET to open should resupply the volume gas loss due to transmucosal exchange, and thereby prevent the development of the threshold underpressure ($\approx$–200 H$_2$O) that is required for fluid transudation and effusion accumulation. However, in a recent experiment that controlled for most of the above listed confounding factors, ME inflation with the inert gas argon, did not prevent the development of OME in monkeys with functional ET obstruction. In this study, an identical experimental model was used, but the inflation protocol was revised to include an earlier onset of treatment (prior to the development of the critical underpressure), a greater inflation frequency (twice per day), and a more standard inflation method (Politzer air bag). The results show that the modifications increased the success rate of inflation for preventing OME from 0% to 50%. The specific protocol modification that resulted in the increased efficacy cannot be addressed using the data from this study. However, theoretical considerations suggest that the improved efficacy was associated with the earlier treatment onset and the more frequent inflations. Since the mucosal exchange rate of argon is similar to that of nitrogen, which constitutes 80% of the inflated air, we would expect a similar success if we had chosen argon as the inflation gas in this study. Further studies are needed to determine the importance of each of these factors, and others yet unidentified to the efficacy of inflation treatments for preventing OME.

To guide further improvements in the treatment protocol, a post hoc assessment was made about possible differences between the ears that did and did not respond to treatment. The specific details on the inflation attempts and outcomes for individual right ears of the experimental group are summarized in the Table. No clear difference was noted between the responding and nonresponding ears for the initial day of inflation or the corresponding level of negative ME pressure. However, more frequent inflation was required in the nonresponding ears as compared with the responding ears. This suggests that...
the 2 groups can be discriminated on the basis of an underlying factor(s) related to mucosal inflammation that influences the rate of ME pressure decrease. This is consistent with the early (day 9) differences between response groups in the degree of inflammation observed using the MRI where the average signal intensity and area of involvement were greater for the nonresponding ears (98 ± 17 U and 29 ± 13 mm², respectively) when com-

Figure 3. Preinflation axial (A) and coronal (B) magnetic resonance images (MRIs) and postinflation axial (C) and coronal MRIs (D) T2-weighted fast echo spin MRI on day 21 for an animal in the inflation group. Note that the high preinflation signal intensity of the tympanum was decreased in the MRI performed 20 minutes after the inflation.
pared with the responding ears (40 ± 2 U and 4 ± 3 mm², respectively).

Of possible concern, the average MRI measures of mucosal inflammation were greater in the 3 nonresponding ears of the experimental group when compared with those in the 6 right ears of the control group. This is consistent with a possible increased risk for acute mucosal inflammation and/or OM during inflation treatments. Although there were no clinical signs of an acute infection in any of the right ears in the treatment group, the single documented case of acute OM with perforation of the tympanic membrane and drainage occurred in a left ear of an animal assigned to the experimental group. It is possible that unwanted nasopharyngeal secretions and pathogens were transmitted along with the air bolus to the ME during inflation, and subsequently initiated a local mucosal inflammatory reaction. While this explanation remains a hypothesis, the possibility of acute OM as an adverse event or complication associated with inflation treatment should be carefully monitored in future clinical trials designed to evaluate the efficacy of that treatment.

Even in the ears with a documented positive response to treatment, continued frequent inflation was needed over the entire follow-up period. This shows that as long as the underlying factor remains unresolved (eg, tensor veli palatini paralysis and ET dysfunction in the current study), prevention of OME requires continual introductions of gas volumes to the ME in sufficient quantities to balance the net volume lost to transmucosal, diffusive exchange. This observation is consistent with the previously reported failure to maintain the clinical and tympanometric improvement in children with OME after stopping the inflation treatments.

Finally, our study addressed the possibility raised in earlier works that the inflation maneuver in itself can cause the false clinical impression of a disease-free ME. Specifically, Gottschalk observed that the tympanum would frequently empty completely after an inflation, only to fill again from the mastoid air spaces after several minutes of pneumomassage. Also, in our earlier monkey experiment, 1 ear with OME that was treated using repeated inflation had tympanometric evidence of improvement (increased compliance, measurable near-ambient pressure), despite the documented presence of ME effusion and inflammation by MRI. These results suggest that inflation can displace effusion from the tympanum to the mastoid and petrous cells. Indeed, that phenomenon may account for the tympanometric and clinical improvements in ME status as well as the high recurrence rate after discontinuing treatment documented in clinical studies of inflation.4 Our data for the 10 pairs of preinflation and postinflation MRIs confirm the postinflation displacement of fluid from the tympanum into the mastoid and petrous cells.

Repeated air inflation was 50% effective for preventing the development of OME in monkeys with functional ET obstruction. Treatment had to be continued throughout the follow-up period to maintain efficacy. Inflated ears may be at increased risk for acute OM secondary to insufflation of nasopharyngeal secretions and pathogens. The inflation maneuver can displace effusion from the ME to the mastoid and petrous cells giving the false impression of a clinical improvement in ME status. Further studies should be conducted to identify the variables affecting the outcome of inflation treatment for OME, to assess the risk of the adverse events of inflation related to acute OM, and to determine the effect of the displacement artifact with respect to cure rates in clinical trials.

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