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The Forced-Response Test Does Not Discriminate Ears with Different Otitis Media Expressions

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Abstract

Objective—Test the hypothesis that the Eustachian tube (ET) function measured using standard manometric test methods is different between groups of ears with tympanostomy tubes inserted for recurrent acute otitis media (RAOM) and for chronic otitis media with effusion (COME).

Study Design—A cross-sectional study of ET function in populations of young children with different otitis media expressions.

Methods—The results for Forced-Response testing of ET function were compared using a general linear model between 37 ears of 26 children and 34 ears of 26 children aged 3 and 4 years old with ventilation tubes inserted for COME and RAOM, respectively.

Results—There were no significant between-group differences in either the active measure of ET opening function, dilatory efficiency, or in the passive measures reflecting the magnitude of the forces that tend to hold the ET lumen closed, the opening and closing pressures and passive transET conductance.

Conclusions—The results do not support the hypothesis that ET closing forces are less in ears with RAOM when compared to ears with COME and, from the results of earlier studies, ears without disease. Both groups were characterized by a low ET opening efficiency (referenced to ears of adults with no disease history). Because both disease expressions present the same pattern of ET dysfunction, other factors are required to explain why a subset of ears with that type of dysfunction develop RAOM, as opposed to the default expression of COME.

Keywords

Eustachian tube; Function Tests; Recurrent Acute Otitis Media; Chronic Otitis Media with Effusion

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CONFLICT OF INTEREST STATEMENT

None of the authors has a conflict of interest to declare regarding this manuscript.

Level of Evidence: 2b –individual cohort study

INTRODUCTION

Otitis media (OM) is a common disease in young children that also affects adolescents and adults. The disease is characterized by inflammation of the middle-ear (ME) mucosa and an effusion within the usually gas-filled ME cavity¹. OM onset can be either symptomatic, acute OM (AOM), or asymptomatic, OM with effusion (OME), and most frequently occurs as a complication of a viral upper respiratory tract infection². AOM is believed to be caused by the transfer of nasopharyngeal pathogens to the ME via the Eustachian tube (ET) with subsequent ME mucosal infection, and OME is believed to be a consequence of ME pressure dysregulation secondary to an ET blockage. Both presentations can evolve to a persistent, relatively asymptomatic, ME mucosal inflammation that can last from months to years, chronic OME (COME). Also, both presentations can exhibit a pattern of frequent recurrences, with recurrent AOM (RAOM) being particularly worrisome to affected patients and their caregivers¹. Extant ME effusion may be accompanied by a significant conductive hearing loss and balance disturbance and, thus, contributes to patient morbidity^{3,4}. At present, there is no highly effective medical or surgical procedure that promotes a long-term cure of COME or prevents RAOM, though surgical insertion of ventilation tubes (VTs), at least temporarily, clears the effusion, resolves the ME mucosal inflammation, and improves hearing and balance⁵.

Past clinical and experimental research evidence a central role for adequate ET function (ETF) in maintaining ME health⁶. The ET represents a potential communication between the ME and nasopharynx for the exchange of gas, pathogens and debris between those compartments. The ET is usually closed which isolates the ME from nasopharyngeal pathogens and pressures and is actively opened periodically by contraction of the Tensor Veli Palatini muscle (mTVP) which allows for gas flow between those compartments to stabilize ME pressure at approximate ambient levels. Bluestone broadly defined poor ET function (i.e. ET dysfunction) as an ET that is either “too open”, facilitating ME access for nasopharyngeal pathogens and pressures, or “too closed”, disrupting normal ME pressure regulation⁷. In his classification, ET dysfunction caused by insufficient closing forces (e.g. a patulous or semi-patulous ET) would promote the development of AOM and its recurrence as RAOM, while ET dysfunction secondary to poor ET opening efficiency causes the development of OME and its persistence as COME. In that regard, the implicit causal relationship between poor ET opening efficiency and OME/COME is well established by experimental^{8,9} and clinical studies^{10–14}, but that between a “too open” ET and risk for AOM and/or RAOM remains largely conjectural⁹.

There are a number of tests designed to evaluate ETF, but relatively few capture information on both the active (e.g. ET opening efficiency) and passive (e.g. ET closing forces) properties of the ET⁶. The Forced-Response test (FRT) originally described by Cantekin and colleagues¹⁰ was designed to assess simultaneously these two classes of ET properties but requires direct access to the ME via a perforation or functional VT in the tympanic membrane which is uncommon in individuals not being treated with VTs for extant or recent disease. However, because VTs are commonly used to treat both COME and RAOM and past studies show that the passive properties of the ET are not different between ears with COME and those without a significant disease history^{10,11,14}, that test can be used to

evaluate the validity of the hypothesized low tubal closing forces in ears with RAOM. Specifically, the hypothesis would be supported if the FRT measures of the tubal closing pressure are less and the transET conductance greater in ears with VTs inserted for RAOM when compared to ears with VTs inserted for COME. Here, we report the results for that comparison between groups of children aged 3 and 4 years old with RAOM or COME and test the stated hypothesis.

METHODS

Our laboratory has been conducting a number of longitudinal studies that include evaluations of ETF by the FRT in children aged 3 through 7 years old with COME and RAOM. For those studies, COME is defined as 3 months of bilateral ME effusion or 6 months of unilateral ME effusion or 3 episodes of OME during the past year, or recurrence of OME after extrusion of previous VTs for OME; RAOM is defined as a history of 3 AOM episodes in 6 months or of 4 AOM episodes in 12 months¹⁵. The two studies from which the present data were extracted excluded subjects if they had cleft palate or other syndromes predisposing to OM, a history of complications of OM or its treatment, or were unable to cooperate with the testing. Both were approved by the Institutional Review Board at the University of Pittsburgh, and written Informed Consent was obtained from a parent before enrolling their child in either study. We abstracted from those databases the first complete FRT done between the ages of 36 to 59 months on ears of children with VTs inserted for either COME or RAOM to include in these analyses.

The FRT protocol was standardized across all studies¹⁰. Briefly, a probe was introduced and sealed into the ear canal ipsilateral to the ET being evaluated. The probe was coupled serially to a flow sensor, pressure transducer and then, via a valve, to a constant flow pump. For testing, the pump delivered ≈ 23 ml/min of air-flow (QO) to the ME. This caused ME pressure to increase and the ET to open passively at a measured pressure (opening pressure-PO). Continued delivery of air-flow resulted in a semi-stable system (i.e. intraluminal ET) pressure (PS) and transtubal air-flow (QS) which was approximately equal to QO. The child was instructed or induced to swallow, an activity associated with mTVP contraction, and the pre-swallow system pressure (PA) and maximum transtubal air-flow during the swallow (QA) were recorded. After the air-flow had returned to the pre-swallow level, the pump was turned off, allowing the ET to close passively while retaining a residual ME pressure (closing pressure-PC). Passive ET conductance (CS; $1/\text{resistance}$) was calculated as QS/PS and active ET conductance (CA) was calculated as QA/PA . The ratio of active to passive conductance (CA/CS) is defined as the dilatory efficiency (DE). When possible, the test was repeated on the contralateral ET using an identical procedure.

All analyses of the FRT pressure-flow waveforms were done independently by two technicians, and these data were reconciled prior to inclusion in the study database. Three FRT passive ET function parameters, PO, PC and CS, and 1 active ET function parameter, DE were analyzed in this report. The ET opening pressure, PO, is a measure of the combined extra- and intraluminal forces acting to maintain a closed ET lumen. The ET closing pressure, PC, is a measure of the extra-luminal force acting to maintain a closed ET lumen. Passive conductance, CS, is a measure of the distensibility of the ET lumen in

response to applied intraluminal pressures. Dilatory efficiency, DE, is a measure of the efficiency of mTVP activity to effect luminal dilation.

Here, we asked two questions. Are the values of the passive FRT parameters different between RAOM and COME ears, and can those parameter when measured in a mixed population of ears accurately assign test ears to their respective group? To address the first question, for each passive function parameter, we used a general linear model to determine if group assignment explained a significant percent of the measured variance in the parameter. There, group was entered as the primary explanatory factor and age, sex, race and laterality were entered as covariates. In a secondary analysis based on our directional hypothesis, we used a 1-tailed Student's "t" test to determine if the values for PO and PC are significantly less and the values for CS significantly greater in the RAOM group when compared to the COME group. For the active function parameter, DE, our hypothesis makes no directional prediction with respect to between-group differences. Because the distributions of DE for each group were highly skewed (not normal), we compared the DE values between groups using a normal approximation to a 2-tailed, non-parametric Mann-Whitney U test. To address the second question, we used a logistic regression model that simultaneously entered the values for the 3 passive function parameters as predictors of group assignment and determined the significance of the contribution of each parameter to group discrimination¹⁴. All analyses were done using the NCSS 2007 statistical software package (Kaysville, Utah).

Under the hypothesis that RAOM ears are characterized by low ET closing forces reflecting a low resistance exchange pathway between the nasopharynx and ME, we expect that PC would be significantly lower and CS significantly higher in the RAOM group when compared to the COME group (which from past studies in adults are not different from a "disease-free" group^{11,14}) and that the model equation including those 3 parameters accurately assigns ears to their respective group. We make no prediction as to the relative values of the DE for the 2 groups but note that, from past research on adults, DE in COME ears was significantly less than that measured in ears without a history of ME disease and DE is an accurate predictor of ear assignment to the COME group in a mixed population of ears with COME and with no significant history of ME disease^{10,11,14,16}.

RESULTS

The study population consisted of 26 children (11 male; 23 white, 3 non-white; avg. age=4.0±0.6 years) with VTs inserted for COME and 26 children (17 male; 20 white, 6 non-white; avg. age=3.7±0.5 years) with VTs inserted for RAOM. ETF was evaluated by the FRT for 37 (16 right) and 34 (19 right) ears of the children in the COME and RAOM groups, respectively.

Table I summarizes the average and standard deviation of the 3 FRT passive function parameters for the 2 groups, and the value of the "F" statistic and probability level for the between-group comparisons when controlled for age, sex, laterality and race. None of the between-group comparisons was statistically significant. Under the directional hypothesis that the average value for the closing pressure is higher and that for passive conductance

lower in the COME group when compared to the RAOM group, the Student's "t" value and associated 1-tailed probability were $t=0.43$, $p=0.33$ for the ET closing pressure and $t=0.01$, $p=0.50$ for the passive ET conductance. None of these differences was statistically significant. The median value and range of ET dilatory efficiency for the COME and RAOM groups were 2.20 (range: 0.07 to 30.24) and 1.81 (range: 0.01 to 85.00), respectively. The distribution of dilatory efficiencies was not significantly different between the groups ($Z=-1.51$, $p=0.13$).

Table II reports the results of the logistic regression analysis. Alone, none of the passive function parameters was a significant predictor of group assignment, the significance level for the model was 0.09, and the percent variance explained by the model was only 4% ($r^2=0.04$). For the assignment of ears to the COME group, the percent correctly classified by the regression equation was 61%, and the sensitivity and specificity of the model for that assignment were 54% and 68%, respectively.

DISCUSSION

Under the tested hypothesis, we expected that there would be significant between-group differences in the FRT parameters reflecting the passive properties of the ET and, specifically, that the ET passive conductance would be higher and the ET closing pressure lower in the RAOM group. We also expected that, when combined, the FRT passive parameters would accurately assign tested ears to their respective group. Our results were not consistent with those expectations and, thus, fail to support the hypothesis. There, none of the 3 passive parameters was significantly different between the RAOM and COME groups despite our reasonable power to detect physiologically meaningful differences. Specifically, the group sample sizes of 34 and 37 ears had more than 80% power to detect a between-group difference of 30% for all passive function variables. One published "pilot" study with smaller group sizes reported that ET passive resistance (1/conductance) was significantly higher, not lower, in ears with RAOM when compared to ears with COME but documented no between-group differences in ET opening and closing pressures¹⁵. Because the passive measures of ETF in adults are not different between ears with COME and those without a significant ME disease history^{11,14,16}, we extend this equality to comparisons of the passive measures of ETF among RAOM, COME and healthy ears. Together, these results suggest that a low resistance ET pathway for gas and material exchange between the ME and nasopharynx is not sole and sufficient for the development of RAOM in young children.

Past research convincingly showed that ET dysfunction in ears with VTs inserted to treat COME is characterized by an inefficient muscle-assisted ET opening mechanism^{10,12,14,16} and animal experiments showed that experimentally debilitating mTVP muscle function caused COME that was not resolved until muscle function was re-established, or VTs were inserted as an alternative pathway for ME pressure regulation^{8,9}. In this study, ET dilatory efficiency, the FRT measure of ET opening efficiency, was not different in the ears with VTs inserted to treat COME or RAOM, and, for both groups, median dilatory efficiency was comparable to that measured previously for 23 adult ears with extant physician-diagnosed ET dysfunction/COME (median DE =1.74, range=0.13 to 7.81) but was less than that

measured previously for 25 adult ears with no concurrent ME disease or past history of OM (median DE =3.68; range=0.04 to 10.35)¹⁴. While the hypothesis tested here does not specify directional differences in dilatory efficiency between the RAOM and COME groups, the similarity of the values for dilatory efficiency when combined with the similarity for measures of the passive function parameters show that ETF, as measured by the FRT, cannot be used to assign ears to RAOM and COME groups.

Accepting a causal role for ETF in the pathogenesis of the different OM expressions, our result was unexpected but can be explained if a secondary factor(s) superimposed on poor ET opening efficiency changes the trajectory of disease pathogenesis from the assumed default condition, COME to RAOM. In that regard, a number of host (e.g. immunological deficiencies) and environmental (e.g. day care) factors have been identified as being more prevalent in the population of children with diagnosed RAOM when compared to age-matched children without significant ME disease. Usually, these factors are considered to be RAOM “risk modifiers”^{5,17,18}. In light of our results, a better approach to identify RAOM risk factors may be to compare the distribution of candidate factors between children with RAOM and those with COME, since this would control for the contribution of ET dysfunction to RAOM risk. The feasibility of this strategy for RAOM risk factor identification is being explored in ongoing studies.

This data interpretation presumes that the FRT captures all information on ETF important for defining the role(s) played by ET dysfunction in OM pathogenesis. In that regard, past studies show that ET dilatory efficiency correlates with the measures of ET opening efficiency available for other tests¹⁴, accurately predicts group assignment in a mixed population of ears with COME and no history of ME disease¹⁴, and, with other factors, identifies ears likely to develop COME recurrence after VTs inserted for the condition become non-functional¹³. For these reasons, we have confidence that dilatory efficiency is a physiologically relevant measure of ETF. In contrast, with the exceptions of extreme variants in ET dysfunction, such as a patulous ET lumen (closing pressure = 0 daPa) or a physically obstructed ET lumen (opening pressure > 1000 daPa), FRT measures of the passive tubal properties have not been clearly related to any pathological expression. Nonetheless, these measures characterize the physical properties of the ET and existing evidence suggests that those properties constrain and limit the muscle-assisted tubal opening efficiency¹⁴. While the parameters of the FRT characterize ETF as currently understood and include measures analogous to those for other existing ETF tests, whether or not they represent a complete description of ETF remains a question open to continued review as our knowledge of this important area of physiology expands.

Here, we also assumed that ETF measured in ears with VTs inserted for RAOM or for COME reflects the pre-VT, constitutive ETF underlying pathogenesis of those disease expressions. However, it is possible that the post-VT, ETF assessments measure a transient state of dysfunction attributable to the extension of the extant ME mucosal inflammation to the ET lumen. If true, the characteristic pattern of ET dysfunction would be similar for ears with VTs inserted for RAOM and for COME since both disease conditions are associated with ME mucosal inflammation. Two lines of evidence argue against this possibility. First, FRTs in adults with healthy ears and no history of ME disease, with healthy ears but with a

history of ME disease in childhood, and with VTs inserted as a treatment for current COME, show similar values for all groups in the passive function parameters but a graded dilatory efficiency from high to intermediate to low, respectively for those groups^{14,16}. The most parsimonious explanation for this finding is that, while the healthy ears with a history of ME disease in childhood had outgrown their constitutive ET dysfunction and COME risk, they retain a low level constitutive dysfunction that is not of sufficient magnitude to provoke pathology. Second, ME mucosal inflammation resolves during the time with functional VTs. If ET dysfunction is a consequence and not the cause of ME inflammation, it is expected that ETF would improve over the period of time with functional VTs. However, a number of longitudinal studies have shown that ETF as measured by the FRT and other tests is not affected by the time with functional VTs^{19,20}.

CONCLUSIONS

The present study of ETF in young children with VTs inserted as a treatment for RAOM or COME showed a similar profile in the two groups. There was no evidence that ETF in RAOM ears was characterized by a pattern indicative of ET closing failure as was hypothesized. Rather, the FRT results suggest a debility in the active, muscle-assisted opening mechanism for both disease expressions. Further studies are needed to explore the patient characteristics which predispose subsets of the ears with poor ET opening efficiency to develop RAOM, as opposed to the expected disease expression, COME.

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TABLE I

Summary Data

		PO23	PC23	CS23	DE23
COME	Avg	324.9	91.6	0.15	3.80
	Std	124.4	59.1	0.08	5.32
RAOM	Avg	302.8	85.6	0.15	4.68
	Std	94.8	40.1	0.06	14.37
Test	F-Value *	1.23	0.43	0.57	0.07
	P-Value	0.27	0.51	0.45	0.79

PO23=opening pressure, PC23=closing pressure, CS23=passive conductance, DE23=dilatatory efficiency

* Calculated after adjusting for age, ear, race and sex

TABLE II

Logistic Regression Analysis

	Intercept	PO23	PC23	CS23	DE23
Beta Coefficient	1.529	-0.003	-0.002	-1.659	0.027
Standard Error	1.669	0.004	0.007	5.061	0.043
Z-Value	0.916	-0.772	-0.320	-0.328	0.628
P-Level	0.360	0.440	0.749	0.743	0.530

PO23=opening pressure, PC23=closing pressure, CS23=passive conductance, DE23=dilatatory efficiency