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Eustachian Tube Function as a Predictor of the Recurrence of Middle-Ear Effusion in Children

Ellen M. Mandel, MD, J. Douglas Swarts, PhD, Margaretha L. Casselbrant, MD, PhD, Kathleen K. Tekely, RN, MSN, Beverly C. Richert, PhD, CRNP, James T. Serokey, MA, and William J. Doyle, PhD

Department of Otolaryngology, Division of Pediatric Otolaryngology, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh School of Medicine, Pittsburgh, PA

Abstract

Objective—In children with ventilation tubes (VTs) inserted for chronic otitis media with effusion (COME), determine if any parameter of Eustachian tube (ET) function measured by the Forced Response Test (FRT) predicts disease recurrence after the VT becomes non-functional.

Study Design—Prospective study of those factors that predict disease recurrence in children with VTs inserted for COME.

Methods—Forty-nine subjects (73 ears; 28 male, 34 white, aged 5.3 ± 1.2 years) with COME had VTs inserted and were evaluable for disease status after the VT(s) became non-functional. The FRT was done when the VTs were patent and results for the last test before the VT became non-functional were used in the analysis. After each VT became non-functional, the children were followed for disease recurrence over a 12-month period. Logistic regression was used to determine if the ET opening pressure, closing pressure and/or Dilatory Efficiency predicted disease recurrence. That model was expanded to include age, sex, race, history of adenoidectomy, previous VTs and the duration of VT patency as potential predictive factors.

Results—Twenty-nine (40%) ears had recurrence of significant disease within 12 months after the VT became non-functional. For the complete logistic regression model, male gender ($P=0.03$), non-white race ($P=0.02$), a shorter period of VT patency ($P=0.01$) and a low Dilatory Efficiency ($P=0.01$) were significant predictors of disease recurrence.

Conclusion—A measure of active ET function, Dilatory Efficiency, but not measures of passive function predicted disease recurrence within the 12 months after the VT became non-functional in children with COME.

Keywords

Eustachian Tube Function; Chronic Otitis Media with Effusion; Recurrence

INTRODUCTION

The middle ear (ME) is a relatively non-collapsible biological gas cavity that must be maintained at near ambient pressures¹. However, ME-ambient pressure equivalence is unstable, being perturbed by changes in atmospheric pressure and by the progressive decrease in ME pressure due to passive diffusive nitrogen exchange between the ME and

Corresponding Author: Ellen M. Mandel, MD Children's Hospital of Pittsburgh of UPMC 4401 Penn Avenue Pittsburgh, PA 15224
Phone: 412-692-6214 FAX: 412-692-6074 Ellen.Mandel@chp.edu.

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local mucosal blood¹. The Eustachian tube (ET) represents a potential communication between the ME airspace and the nasopharynx². While the lumen of the ET is usually closed, the normally functioning ET is opened intermittently by active tensor veli palatini muscle (mTVP) contraction during swallowing and other activities³ to allow gradient-driven gas transfer between the nasopharynx and ME, thereby lessening any extant ME-ambient pressure gradients.

In animals, failure of the ET to open causes the progressive development of ME underpressures that at -200 to -300 daPa (ref ambient) provokes ME mucosal inflammation, capillary disruption and transudation of fluid from the local blood to the ME, a disease presentation similar to that of otitis media with effusion (OME)⁴. Other studies in monkeys show that the disease resolves in concert with the reacquisition of mTVP-assisted ET dilation⁵.

In infants, children and adults with ventilation tubes (VTs) inserted into their tympanic membranes as a treatment for chronic OME (COME), ET function (ETF) tests usually document a severely limited transfer of gas between the ME and nasopharynx during activities associated with mTVP activity⁶⁻⁹. Alternatively, other studies reported an association between COME and the ability to change ME pressure with forcible sniffing, a condition indicating incomplete closure of the ET lumen in COME patients^{10,11}. While these results support an association between ET dysfunction and COME, it is unclear whether the poor ETF is the cause or consequence of COME.

The present study was designed to clarify the directionality of the cause-effect relationship by determining if the results of ETF testing in children with VTs inserted for COME can predict disease recurrence after the VTs become nonfunctional. We tested ETF using a modification of the Forced-Response Test (FRT) which captures information on the magnitude of the pressures that close the ET lumen and on the magnitude of the mTVP-assisted active ET openings¹². The advantages of using the FRT in young children are the relatively short duration of the procedure and the limited participation required of the test subject^{8,9}. Our primary hypothesis was that inefficient mTVP-assisted ET opening is a robust predictor of disease recurrence during the follow-up period.

MATERIALS AND METHODS

We prospectively enrolled children aged 3 to 6 years with VTs inserted for COME in a two-stage study: documentation of ETF while VTs were functional and documentation of disease recurrence after the VTs became non-functional. All children were enrolled within 6 weeks after VT insertion for COME (defined as: 3 months bilateral ME effusion or 6 months unilateral ME effusion or 3 episodes of OME during the previous year, or recurrence of OME after extrusion of previous VTs for OME). Children were excluded 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 during testing. The study was approved by the IRB of the University of Pittsburgh and written Informed Consent was obtained from a parent before enrolling their child in the study.

FRTs were scheduled at 3-month intervals while the VTs were patent. The number of FRT sessions varied among ears (depending upon length of time of VT patency, child cooperation and other factors). For purposes of this analysis, we used the results for the last, most complete test done when the child was free of a cold (closest to the time of VT non-functionality). After each VT became non-functional, the ear was followed monthly for ME status by pneumatic otoscopy and tympanometry for up to 12 months or until ME effusion was observed in the same ear on 3 consecutive visits. We then assigned each ear to one of

three groups: Group-I: little to no ME disease on follow-up (no otitis media or 1-2 visits with otitis media), Group-II: ME effusion diagnosed at 3 consecutive visits during follow-up, and Group-III: ears that could not be assigned to either of Groups I or II for any of a variety of reasons. For our analysis, we focused on those ears with an unambiguous post-VT disease assignment (Groups I and II).

ETF was measured in each ear with a patent VT using a modification of the FRT originally described by Cantekin and colleagues¹². Briefly, a hermetically sealed probe was introduced into the ear canal ipsilateral to the ET being evaluated. The probe was coupled to a flow sensor, pressure transducer and, via a valve, to a constant flow pump. For testing, the pump delivered ≈ 23 ml/min (QO) of air-flow to the ME. This caused the ME pressure to increase and the ET to passively open at a measured pressure (opening pressure, PO). Continued delivery of air-flow resulted in a semi-stable system pressure (PS) at a transET air-flow (QS) approximately equal to QO. The child was instructed or induced to swallow, an action associated with mTVP contraction, and the pre-swallow system pressure (PA) and maximum transET air-flow during the swallow (QA) were recorded. The pump was turned off allowing the ET to passively close while retaining a residual ME pressure (closing pressure, PC). The test was then repeated for the contralateral ET using an identical procedure. These data were processed to calculate the active ($CA=QA/PA$) and passive ($CS=QS/PS$) conductances which are measures of the airflow through the ET during mTVP contraction and under basal conditions, respectively. We then calculated the mTVP Dilatory Efficiency as the active/passive conductance ratio (CA/CS) which measures the fold increase (or decrease) in transET airflow during mTVP contraction. The FRT parameters analyzed for this report included the opening pressure which measures the summed extra- and intra-luminal forces acting to maintain a closed ET lumen, the closing pressure which measures the periluminal pressure acting to close the ET lumen, and the Dilatory Efficiency which measures the efficiency of active, mTVP-assisted tubal dilation.

Analyses of the pressure-flow waveforms for each test were done by each of two technicians and the resulting data were compared and reconciled prior to entry into the database. To analyze these data, we used a series of logistic regression models to determine if the included factors predicted disease recurrence during the follow-up period after the VTs became non-functional. Our first models operated on all ears that achieved a study endpoint and included as candidate predictors of disease recurrence the opening pressure, closing pressure and the Dilatory Efficiency without and then with selected demographic and historical characteristics for each subject. The sample size constrained the number of characteristics that could be included in the model and therefore we chose a subset representing those with the greatest potential to affect disease recurrence. This set included age, sex, race, the number of past VT insertions, the duration of VT patency and if the child had a previous adenoidectomy, an adenoidectomy with VT insertion at the time of entry or no adenoidectomy. Also, we recognize that in subjects with two evaluable ears (bilateral cases), the left and right ears may not be independent observations. Therefore, we reran the full logistic regression model while limiting the data to the ears of subjects with one evaluable ear (unilateral) and the right ears of bilateral cases and then all unilateral ears and the left ears of bilateral cases. Finally, we recognize that Group-I was not homogenous in that ears with no evidence of disease recurrence were combined with those that had one or two months of OM on the assumption that that any short duration OM episode represented the consequences of a recent cold (or allergy) and did not reflect a recurrence of COME by usual definitions. However, this introduced a new variable into the analysis and, therefore, we eliminated those ears with 1 or 2 visits with OM and re-ran the complete logistic regression model. Data were analyzed using the NCSS Statistical Package (Kaysville, Utah). We used the cut-off of 0.05 to assign statistical significance.

RESULTS

Eighty-four children with bilateral VTs were entered; 33 children were withdrawn by their parents or investigators or discontinued follow-up before reaching an endpoint in either ear. Of the remaining 51 subjects with evaluable outcomes, 2 subjects had a clinical course not defined by either Group-I or Group-II and were excluded from the analysis.

Classification as either Group-I or Group-II was done for 73 ears of 49 children (25 with one ear evaluable, 24 with both ears evaluable). Summary data for the demographic and historical characteristics of these 49 subjects are shown in Table I. For those 25 subjects with only 1 ear evaluable, the status of the contralateral ear was: 8 had a VT or perforation at end of follow-up, 12 had not achieved a study endpoint and 5 were not classifiable as either Group-I or Group-II. Of the 73 ears included in the analysis, 44 were classified as Group-I (no OM [n=21] or 1-2 visits with OM [n= 23]), and 29 were classified as Group-II.

In an initial screening of the data, we compared the relevant summary parameter for each of the characteristics listed in Table I between groups using either the Fisher's Exact test (for dichotomous variables) or the Student's t test (for continuous variables). The only significant between-group differences were in the sex ($p=0.02$) and race ($p=0.03$) distributions for the groups.

Summary data for the three FRT parameters and for the subject characteristics included in the subset of tested predictors are reported in Table II for each group. The simple logistic regression model that included only the FRT variables as possible predictors identified Dilatory Efficiency but not the ET opening ($P=0.84$) or closing ($P=0.57$) pressures as a significant predictor of disease recurrence (Beta coefficient =-0.49, Z-Value=-2.64, $P=0.01$).

A summary of the logistic regression analyses for the complete model that included the FRT parameters and the subject characteristics within the subset is presented in Table III. The r^2 for the complete model (Model 1) was 0.50. Low Dilatory Efficiency, short VT duration, being male and being non-white were significant predictors of a greater risk of disease recurrence. For the models operating on the "single ear" data subsets (models II, III), the r^2 was 0.49 for unilateral ears and the right ears of the bilateral cases and was 0.63 for unilateral ears and the left ears of bilateral cases. For both models, the duration of VT patency and the Dilatory Efficiency were retained as significant predictors of COME recurrence, but race and gender were no longer significant, most probably reflecting the loss in statistical power associated with the lesser sample sizes for these models. For the model that controlled for the heterogeneity of Group-I ears by restricting group membership to ears with no evidence of OM during the follow-up period, the r^2 was 0.53 and the logistic regression equation again identified a short duration of VT patency (Beta=-0.29, Z-value=-2.35, $P=0.02$) and a low Dilatory Efficiency (Beta=-1.12, Z-value=-2.09, $P=0.04$) as significant predictors of disease recurrence.

DISCUSSION

The goal of the present study was to test the hypothesis that a parameter of the FRT is a significant predictor of disease recurrence in children with COME during the 12-month period after the VTs inserted for that condition became non-functional. The results for the simple and more complex logistic regression analyses performed on the study data support this hypothesis, finding that Dilatory Efficiency, a measure of the efficiency of mTVP-assisted ET opening, was a significant predictor of group assignment, with lower Dilatory Efficiencies associated with disease recurrence. However, isolating Dilatory Efficiency as the single predictor for disease recurrence in a limited regression model had an r^2 of 0.15 and correctly assigned 77% of the Group II (recurrence) ears but only 45% of the Group I

ears. These results show that Dilatory Efficiency is not sufficiently specific or sensitive to be used alone in the clinical setting for predicting the presence or absence of disease recurrence in individual patients with VTs inserted for COME. Nonetheless, our analyses convincingly demonstrate a role for inefficient muscle-assisted ET opening in the pathogenesis and recurrence of COME in children.

The FRT is one of a number of ETF tests currently in use. Most of these include a parameter that, like the FRT Dilatory Efficiency, reflects the efficiency of muscle-assisted ET openings¹³⁻²². It is not known if these parameters are more or less predictive of disease recurrence in children with COME after their VTs are extruded than Dilatory Efficiency, but this possibility should be explored in future studies. Indeed, it may be possible, and perhaps expected, that combining the results for tests that capture different dimensions of mTVP-assisted ET opening will increase the specificity and sensitivity for identifying patients at risk for disease recurrence to clinically useful levels.

Because the FRT is almost exclusively used in our laboratories and, until recently, our primary focus was on the study of ETF in animal models of COME^{4,5}, the underlying factors that contribute to the intra- and inter-ear variability in Dilatory Efficiency have not been explored. However, for other tests of ETF, both situational and constitutional factors were shown to influence their respective measures of muscle-assisted ET opening and we would expect the same to hold true for Dilatory Efficiency. Of the former, the most well documented is nasal inflammation caused by either upper respiratory virus infection, allergy or sinusitis which was shown to decrease the efficiency of muscle-assisted tubal openings by blocking the nasopharyngeal orifice of the ET and/or by extension of the inflammation to the ET mucosa^{8,17,23-25}. In the present study, we did not test children when a cold-like illness was present and too few children were diagnosed with nasal allergy to determine if this known effect for other measures of ET opening function characterizes Dilatory Efficiency. The best supported constitutional factor is the extant degree of maturation of the ET system. For example, when compared to older children and adults, young children are characterized by poorer muscle-assisted ET openings¹⁵, the mTVP cross-sectional area is much smaller and the vector relationship between the mTVP muscle and the ET are less efficient²⁶. This is an active area of current study by us where we are mapping the change in ETF as measured by the FRT onto the changes in the anatomy of the ET-middle ear system during growth and development. A large number of other factors have been suggested to affect mTVP-assisted tubal opening, but these remain largely hypothetical and without support in humans. For example, the possibility of a myogenic origin for poor mTVP function has been revisited over the years, but this condition appears to be extremely rare and, when present, related to nasopharyngeal tumors invading the mTVP or its nerve^{14,27,28}. Similarly, intraluminal surfactants are expected to improve ET opening efficiency, but there is little evidence from studies in humans to support this contention²⁹.

The full logistic regression model identified four factors that predict COME recurrence: low Dilatory Efficiency, a short duration of time with a patent VT, male gender and non-white race. The inclusion of these four factors in the regression model correctly assigned 82% of the Group II ears and 72% of the Group I ears, a sensitivity and specificity that approach values with clinical utility.

In retrospective studies, the longer the time that VTs remained patent was associated with a lower frequency of OM recurrence after the VTs became nonfunctional. Ahn and colleagues³⁰ reviewed the medical records of 423 children who underwent VT insertion for COME and compared the duration of VT function between those who had undergone one VT procedure and those who had undergone three VT procedures. Mean “tube life” in the single-operation group was 13.6 months vs. 9.9 months in the 3-operation group. Yaman and

colleagues³¹ reviewed a case series of 91 children with COME, and reported the highest rate of disease recurrence was in the group with the shortest time to VT extrusion: recurrence rates of 36.5%, 17.7% and 9.1% were observed in groups with VT patency for <6 months, 6-12 months and >12 months, respectively. These results support our findings and may reflect the relatively long period with an effusion-free middle ear required for mucosal healing within the tympanum and the mastoid during COME as previously reported³²⁻³⁴ or that the disease process underlying COME (e.g., inflammation, allergy) also contributes to early tube extrusion/nonfunctionality.

From our general model, but not the sub-models, males were more likely to have disease recurrence than females. This is not supported in the literature where studies by Ahn and colleagues, Yaman and colleagues and Boston and colleagues found no difference between males and females in disease recurrence^{30,31,35}. However, these negative findings were reported for retrospective studies that did not control for potentially interactive factors or include the tightly scheduled, close prospective follow-up for recurrence used in the present study. For these reasons, the potential significance of our observation of a gender effect, if any, will need to await the results of future studies.

Our model identified “non-White” race as a risk factor for disease recurrence after VT extrusion, but there are few existing data to support or refute this observation. One suggestive retrospective review done by Boston and colleagues reported a greater number of VT insertions in Whites but their logistic model did not identify race as a contributing factor³⁵. Again, our results on a racial effect must await future studies for confirmation or refutation.

Three retrospective studies reported that compared to VT insertion alone, adenoidectomy performed with VT insertion was associated with fewer later VT re-insertions³⁵⁻³⁷. Randomized studies by Maw and colleagues of children aged 2-11 years with COME³⁸ and by Gates and colleagues of children aged 4-8 years with COME³⁹ reported more favorable outcomes with respect to long-term disease resolution for groups treated with adenoidectomy and VT insertion when compared to VT insertion alone. In contrast, more recent randomized studies in younger children aged 12-48 months with recurrent acute OM or COME⁴⁰ or in children aged 24-47 months with COME⁴¹ failed to document an increased benefit of adenoidectomy and VT insertion when compared to VT insertion alone. In the present study, we included within the regression model a variable representing no history of adenoidectomy, a past history of adenoidectomy or adenoidectomy concurrent with the VT insertion for the study endpoint. That variable was not a significant predictor of disease recurrence.

CONCLUSION

The results of the present study identified two robust predictors of COME recurrence after VTs inserted for COME in children are extruded: the length of time that the VT was patent and a measure of active, mTVP-assisted ET opening, the ET Dilatory Efficiency. Minor factors whose significance was lost for restrictive data sets were being male and being non-white, and both were positive predictors of disease recurrence. Adenoidectomy at the time of VT insertion or previous adenoidectomy, number of previous VTs inserted, the child's age at entry, and the ET opening and closing pressures were not significant predictors of disease recurrence. A limitation of the present study is the relatively small sample size which may have decreased our ability to detect significant predictors. Our finding that Dilatory Efficiency is a predictor of COME recurrence should be tested in other cohorts and for prediction of other disease outcomes to establish if this ETF parameter has applications in the clinical setting.

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TABLE I

Characteristics at Entry for the 49 Evaluable Subjects

Characteristic	Total Subjects (N=49)	1 Ear Evaluable (N=25)	2 Ears Evaluable (N=24)
Mean Age (years)	5.3±1.2	5.4±1.2	5.1±1.3
Sex			
Male	28	16	12
Female	21	9	12
Race			
White	34	18	16
African-American	13	6	7
Bi-racial	2	1	1
Past VT Procedures			
0	22	14	8
1	21	9	12
2	4	2	2
3	2	0	2
Adenoidectomy			
None	14	9	5
With Entry VT	23	8	15
Prior to Entry VT	12	8	4
History of sinusitis			
Yes	10	8	2
No	39	17	22
Allergy tested positiv			
Yes	7	4	3
No	42	21	21
Asthma			
Yes	13	4	9
No	26	21	15
Diagnosed with reflux			
Yes	7	4	3
No	42	21	21
Number of children in household:			
1	10	7	3
2-4	36	17	19
5	3	1	2
Family hx nasal allergy:			

Characteristic	Total Subjects (N=49)	1 Ear Evaluable (N=25)	2 Ears Evaluable (N=24)
Yes	25	14	11
No	24	11	13
* Family hx asthma:			
Yes	18	10	8
No	31	15	16
* Family hx ear disease:			
Yes	25	14	11
No	24	11	13
Daily environment:			
Home	13	10	3
Pre-school	17	7	10
Daycare 2-5 child	0	0	0
Daycare >5 child	3	1	2
School	15	6	9
(unknown)	(1)	(1)	0
Breastfeeding hx:			
None	19	11	8
<4 months	13	4	9
>4 months	16	9	7
(unknown)	(1)	(1)	0
Smoke exposure			
None	48	24	24
Mother or father	0	0	0
Full-time babysitter	0	0	0
Part-time babysitter	0	0	0
(unknown)	(1)	(1)	0

VT – ventilation tube

* Family hx = positive for mother, father or sibling

TABLE II

Tested Predictor Variables for Group-I Ears (No Significant Disease) Compared to Group-II Ears (3 Consecutive Months with ME effusion)

	Group-I (N=44 ears)	Group-II (N=29 ears)
Age at Entry (years)	5.1±1.4	5.4±1.0
Prior VT Insertions (mean)	0.75±0.81	0.83±0.85
Prior Adenoidectomy		
None	9	10
With Entry VT	27	11
Prior to Entry VT	8	8
Mean Duration of VT Patency (months)	16.8±6.5	10.7±3.9
Mean Opening Pressure (daPa)	342±118	304±122
Mean Closing Pressure (daPa)	92±55	79±36
Mean Dilatory Efficiency	3.11±2.88	1.28±1.23
Male	19 (43%)	21 (72%)
Race		
White	37 (84%)	17 (59%)
African-American	7 (16%)	12 (41%)

VT – ventilation tube

TABLE III

Summary of the Logistic Regression Analysis for COME Recurrence Listing the Parameter, Correlation Coefficient (Beta), Standard Error of the Coefficient (SE), the Wald Z-Value and Probability Level for All Ears (Model 1), and that Summary for all Statistically Significant Parameters for the Subgroups of all Unilateral Ears and the Left Ears of the Bilateral Cases (Model 2) and for all Unilateral Ears and the Right ears of the Bilateral Cases (Model 3)

PARAMETER	BETA COEF	SE	Z-Value	P-Level
MODEL 1				
Intercept	8.76	3.42	2.56	0.01
Sex (Male)	2.22	1.04	2.14	0.03
Race (non-White)	2.28	1.14	2.01	0.04
# VTs	0.11	0.72	0.16	0.87
Adenoidectomy	-0.88	1.03	-0.85	0.39
Age Entry	-0.82	0.44	-1.87	0.06
Duration VT	-0.32	0.12	-2.63	0.01
Opening Pressure	0.00	0.01	-0.46	0.64
Closing Pressure	0.00	0.01	-0.23	0.82
Dilatory Efficiency	-0.75	0.30	-2.53	0.01
MODEL 2				
Intercept	12.91	5.29	2.44	0.01
Duration VT	-0.44	0.19	-2.37	0.02
Dilatory Efficiency	-0.83	0.40	-2.08	0.04
MODEL 3				
Duration VT	-0.43	0.20	-2.20	0.03
Dilatory Efficiency	-1.14	0.51	-2.25	0.02