TITLE PAGE

Complete title: Eustachian Tube Symptoms are Frequent in Chronic Rhinosinusitis and Respond Well to Endoscopic Sinus Surgery

Authors: Anastasios Maniakas, MD[1,2], Martin Desrosiers, MD, FRCSC[1,2], Marc-Henri Asmar, MD[1], Mohammad Al Falasi, MD[4], Leandra Mfuna Endam, MSc[1], Claire Hopkins, MD, FRCS[5], Carl Philpott, MB ChB, MD, FRCS(ORL-HNS)[6], Sally Erskine MB BS, DOHNS, MRCS[6], Rupert Smith MRes[6], Shaun Kilty, MD, FRCSC[3]

[1]Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), Montreal, QC, Canada; [2]Division of Otolaryngology-Head & Neck Surgery, Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, QC, Canada; [3]Department of Otolaryngology-Head and Neck Surgery, The University of Ottawa, Ottawa, ON, Canada; [4]Department of Otolaryngology-Head and Neck Surgery, Tawam Hospital, United Arab Emirates; [5]Department of Ear, Nose & Throat, Guy's and St Thomas' Hospital, London, UK; [6]Norwich Medical School, University of East Anglia, Norwich, UK.

Statements: This material has never been published and is not currently under evaluation in any other peer-reviewed publication. The authors have received funding through the Canadian Institutes of Health Research (CIHR) & the Fonds de Recherche du Québec-Santé (FRQS).

Presentation: This manuscript was presented at the American Academy of Otolaryngology-Head & Neck Surgery Annual Meeting in San Diego, CA, on September 20th, 2016.

Corresponding author:

Shaun Kilty, MD, FRCSC
Department of Otolaryngology-Head and Neck Surgery
The Ottawa Hospital, University of Ottawa
S3 501 Smyth Rd
Ottawa, Ontario K1H 8L6
Tel: (613) 562-5700
Fax: (613) 562-5323
Email: kiltysj@gmail.com

Short title: Eustachian tube dysfunction in CRS

Keywords: Chronic Rhinosinusitis, Eustachian tube, Endoscopic Sinus Surgery, SNOT-22, Case-control study, Prospective trial

No conflict of interest

ABSTRACT (250 max)

Objective: Symptoms of Eustachian tube (ET) dysfunction are seldom assessed in patients with chronic rhinosinusitis (CRS). The SNOT-22 quality-of-life tool includes two questions that specifically screen for symptoms of ET dysfunction ('Ear Fullness'; 'Ear Pain'). The purpose of this study was to determine the extent to which these ET symptoms were present in patients with CRS, and whether these symptoms respond to endoscopic sinus surgery (ESS).

Study design: Prospective cohort studies

Setting: Secondary and tertiary care centres

Subjects & Methods: SNOT-22 data collected at time of recruitment into IRB-approved clinical trials or case-control studies in CRS was pooled to provide a cross section of the frequency and severity of ET dysfunction in CRS patients. When applicable to the trials, the SNOT-22 was repeated at least 3 months following ESS.

Results: Five trials rendering 131 patients were available for assessment. The control group comprised of 251 participants. 'Ear Fullness' of ≥1 was reported in 80/131 CRS patients compared to 45/251 control patients, (Mean=3.08 vs. 1.84; $p<0.001$). 'Ear Pain' of ≥1 was reported in 39/131 CRS patients compared to 33/251 control patients (Mean=2.31 vs.1.82; $p=0.042$). Following ESS, mean 'Ear Fullness' and 'Ear Pain' scores decreased to 1.17 and 0.73, respectively ($p < 0.001$).

Conclusion: Symptoms suggestive of ET dysfunction are frequent in CRS, and for most patients the symptoms will decrease following intervention, to a level comparable with a non-CRS population. Patients' whose ET symptoms do not respond to ESS may represent a target population for emerging therapeutic options for ET dysfunction.

INTRODUCTION (manuscript max is 3000 words – Intro to Conclusion)

The Eustachian tube (ET) provides the physiological functions of middle ear pressure equalization, protection, and clearance. ET dysfunction can be divided into two categories: functional – defined as the inability to actively dilate the tube; or mechanical – defined as secondary to inflamed mucosa, middle ear disease, hypertrophic adenoids, nasopharyngeal neoplasm, and/or polyps. Tubal integrity and susceptibility to dysfunction are also known to be influenced by allergy and sinonasal disease, especially when these disorders are chronic. Chronic rhinosinusitis (CRS) is one of the most common inflammatory diseases of the nose and paranasal sinuses affecting up to 10% of the population[1,2]. The Sino-Nasal Outcome Test (SNOT-22) is a self-reported symptom-based rhinosinusitis outcome measure tool that is widely accepted and validated for patients with CRS[3]. Patients complete the questionnaire by grading their symptom severity from 0 (not a problem) to 5 (problem as bad as it can be). The SNOT-22 includes two questions related to ET dysfunction, that of "ear fullness" and "ear pain". These symptoms can be quite debilitating to patients[4], leading to increased absenteeism from work or hindered social interactions, and thus deserve further investigation. There have been reports that rhinosinusitis and ET dysfunction can be associated and that endoscopic sinus surgery (ESS) can alleviate such symptoms[5], although it remains to be thoroughly studied.

The aims of this study were to determine the prevalence and severity of symptoms associated with ET dysfunction in CRS patients compared to a control group without known otologic disease or CRS, and to evaluate the evolution of these symptoms in CRS patients following ESS.

METHODS

Chronic rhinosinusitis patients

SNOT-22 data from five institutional review-board-approved prospective clinical trials or case-control studies including both CRS patients with and without nasal polyposis were collected and evaluated. Patients had to have had at least a SNOT-22 completed on the day of surgery to be eligible for this study, while post-ESS SNOT-22 scores were collected from the same patients, when available, at least 3 months following ESS. All patients included in these clinical trials were considered patients at 'high-risk' of CRS recurrence according to our group's previously described criteria[6].

Control group

Control group SNOT-22 data were retrieved from the Chronic Rhinosinusitis Epidemiology Study (CRES)[7,8] and the ongoing Socioeconomic Cost of Chronic Rhinosinusitis Study (SocCoR)[9] database originating in the United Kingdom. Family and friends of patients attending otolaryngology outpatient clinics and hospital and university staff were recruited as controls. This non-CRS population had no self-reported otologic or nasal disease, active treatment for chronic conditions, nor any hospital admissions in the preceding 12 months.

Statistical analyses

All data were tabulated using Microsoft Excel and all statistical analyses were performed using STATA 13.1 (STATACorp LP, College Station, TX). Absolute and relative frequencies are presented for categorical and ordinal variables. A two-tailed Pearson Chi-square or Fisher's exact test was used to compare the prevalence and proportion of ET dysfunction symptoms between CRS and control groups. Comparison of symptom severity and overall SNOT-22 scores between groups and before and after ESS were evaluated using a two-sample Student T-test with unequal variances. For all statistical analyses, a $p<0.05$ was considered statistically significant.

RESULTS

Demographics

A total of 131 patients at 'high-risk' of CRS recurrence were included in the CRS group and completed a SNOT-22 on the day of surgery. The control group comprised of 251 participants having completed the SNOT-22 questionnaire on a single occasion.

Table 1: Demographics and SNOT-22 findings

	CRS group (N=131)	Control group (N=251)	P value
Age (range)	52.7 (21-86)	47.5 (19-80)	
Female	52	143	*<0.001*
Male	79	96	
SNOT-22 (SD)	46.4 (20.6)	12 (13.6)	*<0.001*
No. patients with Ear fullness ≥1 (%)	80 (61.1%)	45 (17.9%)	*<0.001*
No. patients with Ear pain ≥1 (%)	39 (29.8%)	33 (13.2%)	*<0.001*
Mean Ear fullness symptom score if Ear fullness ≥1 (SD)	3.08 (1.25)	1.84 (0.79)	*<0.001*
Mean Ear pain symptom score if Ear pain ≥1 (SD)	2.31 (0.95)	1.82 (0.5)	*0.042*

SNOT-22 according to ear symptom in CRS patients

The mean SNOT-22 score for CRS patients with a score of ≥1 for 'ear fullness' was significantly higher than in CRS patients with a score of 0 (53.2 vs. 35.8; $p<0.001$). Similarly, CRS patients with a score of ≥1 for 'ear pain' had a significantly higher overall SNOT-22 score than CRS patients with a score of 0 (63.4 vs. 39.2; $p<0.001$).

Evolution of 'ear fullness'

Of the 80 CRS patients with a score of ≥1 for 'ear fullness', 66 (82.5%) completed a SNOT-22 score between 3 and 4 months post-ESS. Mean ear fullness score statistically significantly decreased post-ESS to 1.17 (Figure 1), while 78.8% (52 of 66) reported an improvement in their 'ear fullness' score (mean improvement =2.5; range 1 to 5). Five patients (7.6%) reported symptom deterioration.

Evolution of 'ear pain'

Of the 39 CRS patients with a score of ≥1 for 'ear pain', 30 (76.9%) completed a SNOT-22 score between 3 and 4 months post-ESS. Mean ear pain score statistically significantly decreased post-ESS to 0.73 (Figure 2), while 73.3% (22 of 30) reported an improvement in their 'ear fullness' score (mean improvement =2.2; range 1 to 3). Three patients (10%) reported symptom deterioration.

DISCUSSION

The current literature on ET dysfunction symptoms in patients with CRS is very limited. To our knowledge, this is the first study where ET dysfunction symptoms are prospectively evaluated and compared to a control group. Our findings reveal that symptoms suggestive of ET dysfunction are quite frequent in patients with CRS who fail maximal medical therapy and require ESS. More specifically, 'ear fullness' was a reported symptom in close to two thirds of patients, while 'ear pain' was reported in one third of CRS patients. These rates are significantly higher than Stoikes et al.[5]'s previously published findings (42% and 15% respectively). Furthermore, compared to the control group, when present both 'ear fullness' and 'ear pain' were significantly more prevalent and debilitating in CRS patients. Overall, it is clear that the prevalence of ET dysfunction in CRS has been greatly underappreciated, particularly in patients with severe disease.

Our second significant finding is the important treatment effect CRS patients had following ESS. Approximately 75% of reported 'ear fullness' and 'ear pain' had a favourable evolution post-ESS, with a mean improvement of more than 2 points on 5. These findings are slightly inferior to Stoikes et al.[5]'s findings (84.3% and 84%, respectively), although one must

consider the important recall bias and variability of post-ESS response timeframe of their retrospective study. Others have demonstrated the improvement of ear-associated SNOT-22 symptoms without however providing a detailed categorisation[10,11].

Limitations

The proportion of females were significantly higher in the control group, and as it has been described in the literature, females tend to report higher SNOT-22 scores[7]. This unfortunately can hinder our group comparability. However, when males and females average SNOT-22 scores were compared within each group, both CRS and control group females had proportionally higher scores. Overall, the effect of this inter-group difference can only lead to an underestimation of the symptoms in the CRS group, which in turn strengthens the already significant findings we have reported. Furthermore, it is important to note that our follow-up period was short and we therefore are unable assess the long-term effect of ESS on ET dysfunction-associated symptoms.

Future directions

Although this prospective study on ET dysfunction-associated symptoms demonstrates the effect CRS can have on such symptoms, a more thorough evaluation of ET dysfunction with the Eustachian Tube Dysfunction Questionnaire (ETDQ-7)[12] would be most appropriate. Furthermore, what remains to be addressed is the management of CRS patients with persistent and debilitating ET dysfunction symptoms, even following ESS where there remains a prevalence of 7.6% for ear fullness and 10% for ear pain). Alternative management is available and should be considered; one of these may be the novel surgical technique of ET balloon dilatation that has been shown to be a possible therapeutic option[13] but remains to be validated with RCTs and long-term follow-up studies.

CONCLUSION

Symptoms suggesting ET dysfunction have been underestimated in the CRS population, especially in patients with severe disease. Our findings depict the substantial prevalence of 'ear fullness' and 'ear pain' in patients undergoing ESS for CRS, compared to a control population, while also demonstrating the strong positive treatment effect of ESS on these symptoms. We suggest that further study into ET dysfunction in CRS is needed to better understand the origin of these symptoms and to evaluate ideal treatment options for patients whose symptoms do not respond to surgical treatment of CRS.

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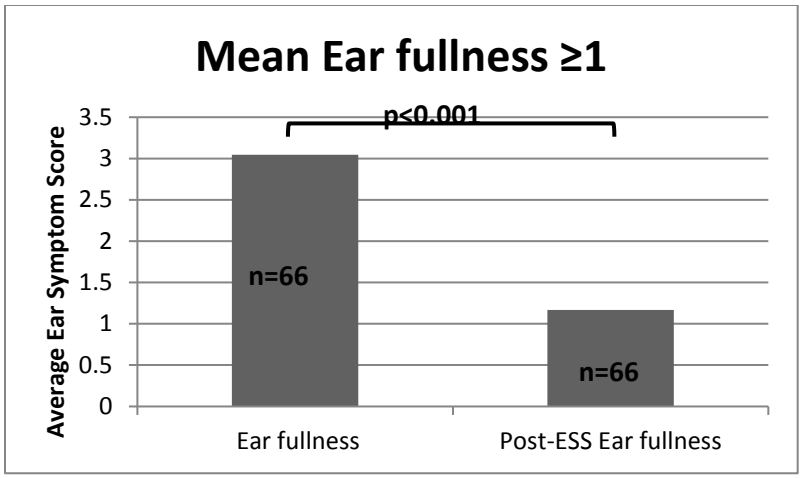
Figure 1: Evolution of mean ear fullness score following endoscopic sinus surgery



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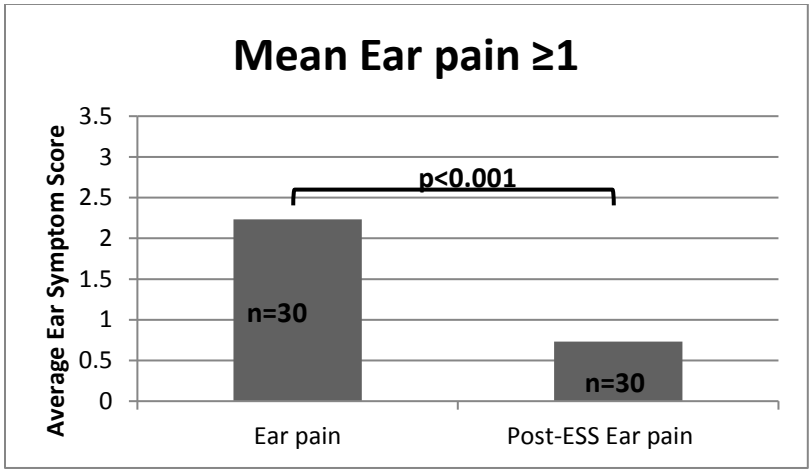

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