Evaluation of Drug Effects on Eustachian Tube Dysfunction in Divers

by

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### Title and Subtitle
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### Summary
Eustachian tube dysfunction (ETD) is associated with middle-ear barotraumas, which is one of the most prevalent medical complications in diving, aviation forces, and hyperbaric medicine. The purpose of this trial was to determine the efficacy of various drugs to decrease the incidence of ETD. Acetylcysteine, surfactant, pseudoephedrine, and oxymetazoline were tested against nasal saline mist in a subject-blinded, randomized trial. Divers were administered the drugs just prior to repetitive bounce dives while breathing oxygen or air in separate trials. Effectiveness was assessed via subjective difficulty to clear (holds on descent), ET opening pressures, and measurements elicited from a 9-step inflation/deflation tympanogram. There was considerable variability in the outcomes of each analysis that resulted in no consistent differences being established between the drugs evaluated. No drug had evidence to support recommendations for or against its use in preventing ETD. Some of the drugs tested may yet show beneficence if evaluated in another experiment designed to address the confounding factors encountered during this study.

### Subject Terms
Eustachian tube dysfunction, diving, hyperbaric medicine, aviation forces
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ABSTRACT

Problems associated with the Eustachian Tube (ET) can result in significant impacts to diving, aviation forces, and hyperbaric medicine. Eustachian tube dysfunction (ETD) is associated with middle-ear barotraumas, which is one of the most prevalent medical complications in the above arenas. The purpose of this trial was to determine the efficacy of various drugs to decrease the incidence of ETD. Acetylcysteine, surfactant, pseudoephedrine, and oxymetazoline were tested against nasal saline mist in a subject-blinded, randomized trial. Divers were administered the drugs just prior to repetitive bounce dives while breathing oxygen or air in separate trials. Effectiveness was assessed via subjective difficulty to clear (holds on descent), ET opening pressures, and measurements elicited from a nine-step inflation/deflation tympanogram. There was considerable variability in the outcomes of each analysis that resulted in no consistent differences being established between the drugs evaluated. No drug had evidence to support recommendations for or against its use in preventing ETD. While the results of this study failed to demonstrate efficacy for any given medication, some of the drugs tested may yet show beneficence if evaluated in another experiment designed to address the confounding factors encountered during this study.
ACKNOWLEDGEMENTS

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INTRODUCTION

The sequelae arising from an inability to equilibrate middle ear pressure can severely undermine the performance of individuals engaged in the fields of diving, aviation, and hyperbaric medicine. Middle Ear Barotrauma (MEBT) or the accepted colloquial terms, “middle ear squeeze” or “barotitis media,” is the most common medical complication in diving, aviation, and hyperbaric medicine.1

The Eustachian tube (ET) connects the middle ear with the nasal cavity. It contains a mucosal layer similar to the respiratory mucosa and is surrounded by muscular and cartilaginous components.2 The ET is normally in a collapsed configuration (closed under the influence of surface tension),3 protecting the middle ear from nasopharyngeal secretions, but opens to ventilate the middle ear and allow pressure equilibration and exodus of middle ear secretions. Eustachian tube dysfunction (ETD) is the terminology employed when one is unable to easily open the ET to facilitate its ventilatory functions, accompanied by pathological consequences such as barotraumas (injury from exposure to pressure variations in diving and aviation) resulting from the lack of pressure equalization in the middle ear.

The ET opening pressure (ETOP) is intimately related to surface tension, a physical property highly influenced by the biochemical compound surfactant, noted to be present in the ET.3 Thus, surfactant is responsible for maintaining ET patency and facilitating middle ear drainage. The physicochemical properties serve a similar role as performed in the lungs to reduce the alveolar (lung sacs) opening pressures. This observation supports the hypothesis that exogenous surfactant may potentiate middle ear equilibration as a result of a reduction in ETOP.

Failure to equalize middle ear pressure hinders mission effectiveness as it results in temporary or permanent loss of a team member. There are many young, highly motivated individuals who are denied initial entry into the diving program due to ETD. Thus, an inordinate number of otherwise highly qualified individuals are unable to pursue these vocations. Divers afflicted with ETD must often abort a mission due to the inability to equilibrate middle ear pressures, particularly when performing repetitive diving or diving on 100% oxygen.

Quite sobering is the increased sub-clinical expression of ETD reported after repetitive diving. Previous studies noted progressive decrements in daily tympanometric measurements reflecting reduced middle ear pressures, supporting sub-clinical ETD in their investigation with recreational divers.4 Therefore, it appears that the risk of MEBT increases after repetitive diving and that ETD develops in an insidious fashion due to repeated sub-clinical insults culminating in the precipitous onset of a middle ear squeeze.

The risk of MEBT increases with diving on hyperoxic mixtures and is of profound relevance to those engaged in diving with the closed circuit pure oxygen underwater breathing apparatus. Abnormal tympanometry results after diving on pure oxygen, manifested as negative middle ear pressures, middle ear effusions, and decreased eardrum compliance.5

One etiology speculated for the development of hyperoxic mediated ETD is a decrease in surfactant secretion, now known to be instrumental in the proper functioning of the ET.6,7,8 Precedence for these assertions have been established in the pulmonary arena. Correlations have
been drawn between hyperoxic-mediated decreases in pulmonary surfactant secretion and pulmonary damage.\textsuperscript{9}

Currently, the standard treatment and prophylaxis against MEBT involves the administration of oral and/or topical decongestants (orally administered pseudoephedrine (ie, Sudafed\textsuperscript{®}) and intranasally administered topical decongestants such as oxymetazoline (ie, Afrin\textsuperscript{®}). These medications serve to shrink the nasopharyngeal mucosa, potentiating the opening of the ET passages, thus facilitating middle ear and sinus ventilation and pressure equalization. Despite the universal utilization of these medications, their efficacy in the treatment and prophylaxis of MEBT is not well documented. In fact, oral decongestants such as pseudoephedrine have not consistently been shown to be efficacious in treating or preventing otitis media.\textsuperscript{10} There has been no documented efficacy with topical decongestants either. Surprisingly, there is a paucity of data documenting any evidence-based support for the use of these agents for diving as a means of facilitating middle ear equalization.

Similar results have been found in measuring the equivocal efficacy of the oral decongestant, pseudoephedrine, and related alpha-agonists in mitigating ETD.\textsuperscript{11} There has been a demonstrated significant reduction in both incidence and severity of MEBT in novice divers taking Sudafed\textsuperscript{®}.\textsuperscript{12} A demonstrated reduction in MEBT in air travelers taking pseudoephedrine prior to flight departure has also been noted.\textsuperscript{13} However, administration of Afrin\textsuperscript{®} nasal spray demonstrated a lack of efficacy in preventing barotraumas prior to air travel.\textsuperscript{14} Furthermore, no efficacy was found in reducing barotraumas in subjects taking Afrin\textsuperscript{®} nasal spray prior to hyperbaric chamber exposure.\textsuperscript{12} From the vast number of conflicting studies, it is difficult to conclude that decongestants are effective. Although decongestants have a lack of evidence in their favor in general, the literature seems to favor oral agents over the topical.

A potential complication resulting from decongestant utilization concerns rebound congestion leading to barotrauma upon ascent, which may pose a serious threat to diver health and safety.\textsuperscript{10} This rebound phenomena is most pronounced at the nasopharyngeal orifice (ET opening) and impedes the evacuation of gas upon ascent preventing proper equalization of middle ear pressure. A theoretical utility of surfactant resides in its theoretical dissemination over the entire ET surface, which would improve ETOP for both ascent and descent.

To fill the gap in evidence based support for the use of oral and nasal alpha-agonists (eg pseudoephedrine and oxymetazoline) in potentiating ET opening, middle ear pressure equilibration, and resistance to MEBT in diving, these medications were evaluated alongside the novel medications surfactant and acetylcysteine.

An inordinate number of missions are undermined or aborted due to the inability to equilibrate middle ear pressures secondary to upper respiratory infections or to concomitant medication use to combat allergies, motion sickness, and musculoskeletal pain. Numerous military missions require breathing elevated oxygen concentrations or performing sequential dives, which could potentiate ETD predisposing to MEBT as implied above. Efficacious administration of a medication via a simple, portable, familiar, and expedient route as a prophylaxis and/or treatment harbors enormous potential.
METHODS

A total of 8 US Navy trained male divers participated in a subject-blinded, random order, multi-arm (Air and O₂) trial. This study investigated the relative efficacy of intra-nasally administered (1) surfactant, (2) acetylcysteine, (3) oxymetazoline, and an oral administration of (4) pseudoephedrine versus (5) nasal saline mist on both the objective and subjective ability to equilibrate the middle ear pressures during repetitive, multi-day diving and diving on hyperoxic mixtures. The surfactant was provided by “Device and Pharmaceutical R&D, Ross Products Division, Abbott Laboratories.”

All subjects demonstrated ability to equalize the pressure in the middle ear via whatever method worked best for them. Subjects were instructed to use this preferred method consistently during all dives and testing. All tests were performed in the Genesis Chamber at Naval Submarine Medical Research Laboratory in Groton, CT. Dives were conducted within a water tank inside the hyperbaric chamber maintained at a temperature of 16 degrees Celsius to properly simulate the open water diving exposures to which operational divers will be subjected. During the dives, subjects were in a vertical position with head up and completely submerged. Divers wore 7-mm dive suits to stay warm and remained un-hooded throughout the experiment. No subject experienced additional hyperbaric exposure outside of the trial, during the trial, or 2 days prior to the consecutive diving days. Holds initiated by divers during descent were recorded for comparison.

All subjects were subjected to the Nine Step Inflation/Deflation Tympanogram (NSI/DT) prior to and immediately following each dive. The NSI/DT was conducted as delineated and consisted of measuring middle ear pressures at baseline and after applying both negative and positive pressure into the external ear canal. When the negative or positive pressure is applied subjects swallow three times, possibly allowing for passive equalization of the middle ear. Thus, three pressures are produced: one at baseline, another measurement following swallowing during negative pressure application, and the last measurement following swallowing during positive pressure. NSI/DTs were conducted with a Grason-Stadler GSI-33 Middle Ear Analyzer.

After completion of the NSI/DT, the subjects proceeded with measuring ETOP. ETOP was measured with a device assembled locally at NSMRL. The instrument measured the sound output of a speaker held up to a nostril via a microphone with associated pre-amplifier in the ipsilateral external auditory canal. When the subject was instructed to make one clearing attempt, the device noted any changes in the recorded intensity of the sound due to the opening of the ET. The assumption is that the opening of the ET allows for increased conductance of the sound from the nostril to the external ear canal. This increase in conductance is detected as a sudden increase in the intensity of sound. The microphone and speaker were then switched to the

Figure 1 Shows a subject performing a clearing maneuver for Eustachian Tube Opening Pressure measurement. Note the microphone in the external ear canal, along with the speaker (right nostril) and pressure transducers obstructing the nostrils.
opposite ear canal and nostril, respectively and the process was repeated. During each clearing attempt, a pressure transducer (capable of measuring up to 200cm of water) was held in the nostril opposite the speaker which served to close off the nostril for the clearing attempt and to record the pressure that would correlate to the increase in sound intensity (Figure 1). A bandpass filter was used to isolate the frequencies related to the sounds generated by the speaker. After overlaying the data obtained about the sound intensity and the recorded pressure in a graphical format, the value of the pressure at the sharp increase in sound intensity was recorded as the ETOP. Each ear had one “clearing attempt” against a pressure transducer, starting always with the left ear first, followed by one attempt with the right ear. This is significant since repeated equalization maneuvers may decrease ETOP. The pressure measurement at the increase in sound was the measure for ETOP (Figure 2).

An ER-10C microphone (produced by Etymotic Research) and ER-6 isolater earphones (also produced by Etymotic Research) were used in conjunction with a Validyne model DP103-40 pressure transducer (by Validyne Engineering Corp). The speaker frequency utilized was 10 kHz and a laptop captured the raw sound data from the microphone. The source sound level was never measured, but as part of the data collection the received sound was recorded as shown below. The device was controlled through a laptop with an A/D card sampling at 44 kHz. The data was analyzed in sequential, non-overlapping blocks of 1024 points, an FFT was applied to each block of data, the FFT identified the interval containing the 10 kHz signal, and the magnitude of that peak is computed and displayed.

![Graph](http://archive.rubicon-foundation.org)

**Figure 2** displays the ideal tracing obtained for a Eustachian Tube Opening Pressure (ETOP). This graph represents both the sound intensity and pressure on the y-axis with time on the x-axis. The pressure at the point where the sound suddenly increases corresponds to the ETOP. This is assumed to be evidence of the ET opening and allowing the sound to conduct more effectively to the external ear canal.
Dives took place over three consecutive days for ten weeks for a total of thirty diving days. Divers performed one dive on each day for a total of three consecutive diving days per week. This schedule of repeated daily dives imposes stress on the middle ear, potentiating the ability to discern an effect in treatment and increasing the ability to detect a difference in treatment efficacy. On the three consecutive dive days subjects were administered the same drug, and each set of three dives had at least four days in between them. The dives began with the NSI/DT and ETOP. The NSI/DT and ETOP took place before and after each subsequent dive. It should be noted that although some of the diving was performed breathing 100% oxygen, all testing was done in room air. Not all divers completed all profiles resulting in an unbalanced repeated measures design. The maximum number of ETOP measures for any subject was 2 (ears) by 2 (gases) by 5 (drugs) by 3 (dives) by 2 (tests [pre-dive and post-dive]) = 120. The order of drug administration was randomly assigned to each diver and the drug order for each diver was unique.

The dive profile for the air dives consisted of an excursion to 60 fsw, holding that depth for two minutes, followed by ascent to the surface. Descent rates were 60 ft/min and ascent rates were 30 ft/min. Each dive profile consisted of four identical excursions to 60 fsw with one minute surface intervals between repeat excursions. The oxygen arm of this study consisted of dives breathing 100% oxygen that were identical except the depth excursions were limited to 15 feet.

All dives required a nasal inhaler and pill administration so subjects were unaware of the type of medication being administered to satisfy comparisons of medication administration. Trials not utilizing oral pseudoephedrine required a placebo pill consisting of lactose fashioned to the shape and color of a pseudoephedrine tablet. The original experimental design envisioned using nasal saline mist as the nasal inhaler placebo condition, so it was used both with the oral pseudoephedrine condition as a “control” for nasal inhaler use, as well as a treatment condition by itself with accompanying administration of the oral lactose placebo pill for a placebo condition. Thus, the “saline” condition consists of a lactose placebo pill and nasal saline, while the “pseudoephedrine” condition is oral pseudoephedrine with nasal saline. Some comparisons are done to saline since it was intended to be the control condition.

**Surfactant** (ie, Survanta®) was administered by nasal inhaler so that two sprays with approximately 100 µl/dose in a 0.9% saline solution were delivered to each nostril. The product was refrigerated prior to use at (2-8°C), warmed 20 minutes prior to administration, and swirled (not shaken) for reconstitution. When administering via the nasal inhaler, the bottle was oriented horizontally with the head vertical to optimize delivery to the ET. **Acetylcysteine** (ie, Mucomyst®) was administered by nasal inhaler, two sprays in each nostril, with each spray containing 0.1 mL of a 10% solution, 20 mg per nostril. **Oxymetazoline hydrochloride 0.05%** was administered by nasal inhaler, two sprays in each nostril. The **pseudoephedrine 60 mg tablet** was taken orally. Oral placebo administration consisted of swallowing one lactose tablet (identical in appearance to pseudoephedrine). Nasal saline was administered by two inhaler sprays of 0.9% sterile saline solution into each nostril. All nasal medications were administered approximately 15 minutes prior to the dive. All pills were administered at least 30 minutes, and no greater than 60 minutes, prior to the dive.
All holds and subjective difficulty during the dives were logged for subjective data. Data analysis was done using SPSS 13.0. Type I error probability acceptance was set at .05 and all significance tests were nondirectional.
RESULTS

Completed Profiles

Subjects consisted of eight male, Navy-trained divers. Seven subjects tested all medications on oxygen dives but only four divers completed the air dives. We have a partial data for two subjects on air and one on oxygen dives because not all medications were tested in these individuals. There were two subjects who did no air dives and two subjects who only completed part of the set for the air dives. Thus, there were only eleven subject-gas conditions where a full data set for all five drugs was available and where all drugs could be compared.

The two partial data sets in air tested only oxymetazoline / surfactant and saline / surfactant. The one partial data set diving oxygen tested saline, surfactant, pseudoephedrine, and oxymetazoline conditions, missing only the acetylcysteine condition. Since each full data on a dive tests 5 drugs, and we have 11 complete sets, we can expect to see 55 subject-drug-gas conditions. Add that with the partial data set described above and we have data testing 63 subject-gas-drug conditions. In an oxygen environment we have 39 subject-drug conditions tested among 8 subjects and in an air environment we have 24 subject-drug conditions among 6 subjects.

Each “dive” consisted of 3 consecutive days of diving and data were obtained each day on each ear. This means that for the 63 subject-gas-drug conditions, there were 126 tested ears for the ETOP and tympanometry because each ear (right and left ears) was measured individually. This is important to note because one would expect each individual ear to produce the least amount of variability across the different drugs and 3 consecutive diving days when the subject and gas conditions are kept the same. Even within subjects, variability between ears could be pronounced as some divers describe a “problem ear” or consistent difficulty clearing on one side only. Between subject variability is considerable, as some divers were able to consciously open their ETs and others struggled fervently only to have a dive conclude in an abort secondary to a hold. Thus, in some of the following analysis, comparisons between drugs were made within individual ears instead of across subjects or gases to try to reduce variability.

<table>
<thead>
<tr>
<th>Diver Ear</th>
<th>Drug</th>
<th>Dive</th>
<th>Test</th>
<th>Gas</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 right</td>
<td>acetylcysteine</td>
<td>3</td>
<td>post dive</td>
<td>air</td>
</tr>
<tr>
<td>6 left</td>
<td>saline</td>
<td>3</td>
<td>pre dive</td>
<td>oxygen</td>
</tr>
<tr>
<td></td>
<td>saline</td>
<td>3</td>
<td>post dive</td>
<td>oxygen</td>
</tr>
<tr>
<td>6 right</td>
<td>saline</td>
<td>3</td>
<td>pre dive</td>
<td>oxygen</td>
</tr>
<tr>
<td></td>
<td>saline</td>
<td>3</td>
<td>post dive</td>
<td>oxygen</td>
</tr>
<tr>
<td>7 left</td>
<td>oxymetazoline</td>
<td>2</td>
<td>post dive</td>
<td>air</td>
</tr>
<tr>
<td></td>
<td>oxymetazoline</td>
<td>3</td>
<td>post dive</td>
<td>air</td>
</tr>
<tr>
<td></td>
<td>surfactant</td>
<td>3</td>
<td>pre dive</td>
<td>air</td>
</tr>
<tr>
<td></td>
<td>surfactant</td>
<td>3</td>
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<td></td>
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<td>3</td>
<td>post dive</td>
<td>air</td>
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<td>3</td>
<td>pre dive</td>
<td>air</td>
</tr>
<tr>
<td></td>
<td>surfactant</td>
<td>3</td>
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<td>air</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 1 displays the 13 subject-gas-drug conditions in which the Eustachian Tube Opening Pressure was not able to be accurately measured.

Missing or Bad ETOP

In addition to the incomplete profiles, 13 ETOP levels were either missing or unmeasurable (eg, pressures greater than 400 cm H₂O are considered invalid). These are shown in Table 1.
**Diver and Ear Cases**

While there is no known rationale to expect ETOP to differ between left and right ears, a linear mixed model ANOVA test with ear treated as a fixed factor and diver as the random factor was performed to determine if, when including all tests, there was a significant difference between ears (interpretation of results is similar to a dependent t-test however the mixed model allows for missing data). This test confirmed there was no overall significant difference between left and right ears when matched by diver, gas, drug, dive (1, 2, or 3), and test (pre- or post-) condition ($F_{7, 734} = .641; P = .42$). Therefore, for all subsequent analyses each case represents a diver and ear combination thereby essentially doubling the initial sample size. No interaction effects between ear and other variables were examined as interpretation of these would be difficult without supporting rationale.

Figure 3 displays all observed ETOP measures by subject and ear that are included in the data analyses and it can also be used to make intra- and inter-subject comparisons.

**ETOP Analysis**

**Observed and Delta ETOP**

Using the linear mixed model (LMM) procedure, significance tests were performed to determine if the observed ETOP varied by the main effect of test; the 2-way interactions of gas by test, drug by test or dive by test; the 3-way interactions of gas by drug by test, gas by dive by test, or drug by dive by test; and the 4-way interaction of gas by drug by dive by test. It is of particular interest whether or not repetitive diving (ie, several excursions within a single dive or diving on 3 sequential days) or the drugs administered had an effect on ETOP. Only effects including the test term were examined to account for pre-dive and pre-drug differences. It should be noted that all pre-dive ETOP measures were done before any drug administration so any pre-dive measure is also a pre-drug measure. The LMM was chosen over the general linear model (GLM) because this procedure allows for unbalanced designs and uses all available information for each diver and ear combination in contrast to the GLM that would exclude all diver and ear cases found to have any missing or incomplete data. In addition, the LMM, which is an expansion of the general linear model, allows the dependent variable (change in ETOP ($\Delta$ETOP)) to exhibit within-subject correlations and non-constant variance across subjects (thereby reducing the stringency of the homogeneity of variance and sphericity assumptions). When entering the model diver and ear were treated as a random factor (to account for subject to subject variation across factor levels as opposed to case to case variation) and gas, drug, dive, and test were entered as fixed factors. Missing values were assumed missing completely at random (MCAR) and the Satterthwaite approximation for degrees of freedom was used. Where mean differences were found, significance levels for multiple comparisons used the Bonferroni adjustment which uses the familywise error rate. Interpretation of significance tests are equivalent to a repeated measures ANOVA test.
Figure 3  Observed Eustachian Tube Opening Pressure for all measures included in the analyses.
Similar procedures were followed for the delta ETOP analysis, where $\Delta$ETOP is equal to [post-dive ETOP – pre-dive ETOP] (a negative value indicates a decrease or improvement in ETOP) for each gas by drug by dive condition. For $\Delta$ETOP, a reduced LMM was entered where gas, dive, and drug, were the fixed factors and diver and ear was again a random factor. Tests of fixed effects were done for the main effects of gas, drug and dive; the 2-way interactions of gas by drug, gas by dive, and drug by dive; and the 3-way interaction of gas by drug by dive.

To determine whether the residuals of the final predicted values of both the observed and delta ETOPs were normally distributed, the residual’s observed cumulative probability was plotted against the expected cumulative probability for the normal distribution. Figures 4 and 5 show that the residuals for both models match the normal distribution as all points cluster around a straight line.

![Figure 4 Normal probability plot of cumulative proportions for observed Eustachian Tube Opening Pressure. Because factor level samples are small, residuals for all factor levels are combined. No serious departures from normality are indicated.](http://archive.rubicon-foundation.org)

![Figure 5 Normal probability plot of cumulative proportions for $\Delta$ETOP. Because factor level samples are small, residuals for all factor levels are combined. No serious departures from normality are indicated.](http://archive.rubicon-foundation.org)

### Observed ETOP

For the linear mixed model, the main effect for test ($F_{1,668} = 1.43; P = .23$) was not significant; however, interaction effects were found for gas by test ($F_{2,669} = 27.52; P < .001$) and drug by test ($F_{8,668} = 4.05; P < .001$). For the gas by test interaction, pairwise comparisons for test effects were found to be nonsignificant; however, pairwise comparisons for gas showed mean ETOP measured before the air dives was higher than the mean ETOP measured before the oxygen dives when subjects were also breathing air. When ETOP was measured after diving, mean ETOP for post-air dives were higher as compared to ETOP measured post oxygen dives (both p-values were at .001 or less). While both differences were significant, Figure 6 shows the 95% confidence levels (CI) slightly overlap for the pre-dives but not the post-dive.
Figure 6  Gas by test interaction. Post hoc showed mean pre-air was significantly higher than mean pre-O2 and post-air was significantly higher than post-O2. Observed means are displayed; significance test is based on estimated marginal means; n = 8 ears for air; n = 16 ears for O2.

For the drug by test interaction shown in Figure 7, the only test effects that were found were for the oxymetazoline condition where the pre-dive ETOP was found to be significantly higher ($P = .04$) than post-dive ETOP. When pairwise comparisons were done for drug effects for pre-dives, the acetylcysteine condition was found to have significantly lower ETOPs than all other drug conditions (result could be spurious). For post-dives, the saline condition was found to have significantly higher mean ETOP than the acetylcysteine condition ($P = .002$).

For the 3-way and 4-way interaction tests of fixed effects only the test by drug by dive interaction was found to be significant ($F_{16, 668} = 2.47; P = .001$) (Figure 8). For test effects, only the first dive under the acetylcysteine condition showed a significant effect where the ETOP measured after the dive was significantly higher ($P = .01$). For drug effects, only pre-dive 1 showed any differences where again mean ETOP measured for the acetylcysteine condition was found to be significantly lower than all other pre-dive 1 drug conditions ($P$-values from .007 to $< .001$). The pre-dive 1 ETOP for oxymetazoline was also significantly higher than pre-dive 1 pseudoephedrine ($P = .048$). For dive effects, under the pre-dive oxymetazoline condition, dive 1 was shown to have significantly higher ETOP than both dive 2 and 3 ($P < .001$ and $P = .04$, respectively). In addition, for the post oxymetazoline condition, dive 1 ETOP was significantly higher than dive 2 ($P = .04$). The only other dive effects were found for the acetylcysteine condition where the mean for dive 1 was significantly lower than the mean ETOP for dives 2 and 3 ($P = .02$ and $P = .001$, respectively).

All significance tests are based on marginal or predicted means; observed means are plotted. No other significant effects were found.
Figure 7  Drug by test interaction for mean Eustachian Tube Opening Pressure. Oxymetazoline pre-dive ETOP was significantly higher than oxymetazoline post-dive. Pre-dive acetylcysteine was significantly lower than all other pre-dive drug conditions. Post-dive acetylcysteine was significantly lower than post-dive saline.

Figure 8  Test by drug by dive interaction for mean Eustachian Tube Opening Pressure.
Delta ETOP

To determine if the magnitude of change from pre- to post-dive ETOP differed between gases, drug conditions, or dives, a linear mixed model was performed. Similar to the LMM for observed ETOP, the fixed factors were gas, drug, and dive, and diver and ear was entered as a random factor. No differences for any main effects were found to be significant. The only significant interaction was found for the drug by dive interaction \( (F_{8,326} = 2.35; P = .02) \) shown in Figure 9. Multiple comparisons for drug effects showed that for the first dive, the mean change in ETOP when acetylcysteine was administered was significantly larger (worsened) than the mean change in ETOP for oxymetazoline (improved) \( (P = .001) \). When dive effects were examined, for the acetylcysteine condition, changes in the dive 1 ETOP, were significantly larger that those found for dive 2 \( (P = .05) \) and dive 3 \( (P = .001) \); dives 2 and 3 showed post-dive improvement in ETOP, but dive 1 showed it worsened. Overall, most mean changes ETOP showed improvements (Figure 10).

![Figure 9 ΔETOP for drug by dive interaction. Means for gas conditions are collapsed. Error bars eliminated for clarity.](http://archive.rubicon-foundation.org)

Tympanometry Measures

Initial Tympanometry Pressures
In this analysis, the initial pressures on the NSI/DT were compared across dives 1, 2, and 3 within a subject. The expectation in the absence of any treatment was to observe an increasingly negative pressure each day correlating with increasing dysfunction and inflammation of the ET as a result of repetitive diving. There were only three subjects out of the eight whose pattern was consistent with this on saline. Without meeting this baseline criterion, it is difficult to definitively compare drugs to the saline condition. In all 3 cases where this comparison was made, there was
no drug that was clearly able to affect the pressures behind the TM on subsequent days. All of the drugs provided very erratic results between each day improving on saline in one interval while worsening the negative pressure drastically in the next interval. There was no superiority among any of the drugs when compared to saline.

![Figure 10](http://archive.rubicon-foundation.org)

**Figure 10** ΔETOP for drug by dive by gas interaction. This interaction was not significant; but the figure gives a good overview of the direction of the mean changes.

**Nine Step Inflation/Deflation Tympanogram (NSI/DT)**

In this analysis, subjects were compared with the number of “passed” NSI/DT or specifically, the number of subjects that were able to equalize the middle ear pressure by at least 10 decapascals (daPa) when a positive or negative 200 daPa pressure was applied to the external ear drum and the subject swallowed 3 times. Passing once (when the negative or positive pressure was applied) resulted in a value of “1” and passing twice (when both negative or positive pressure were applied) resulted in a “2.” No passes resulted in a “0.” Essentially, the ability to easily equalize the pressure suggests good ET function when compared with those unable to equalize.

The difference in the number of passes, or pressure grade, pre- and post-dive on the trial medications resulted in improvement (+), worsening (-), or staying the same (0). To compare the pre-dive pressure grade to the post dive pressure grade, chi-square goodness-of-fit tests were performed to determine if the frequency of occurrence for a negative, positive, or 0 change was more than what would be expected by chance fluctuation when assuming each scenario was equally likely to occur. Using SPSS Exact Tests\(^\text{15}\), separate chi-square tests were done for each drug and gas treatment combination. Standardized residuals (SR) were calculated if the analysis resulted in a significant chi-square (a priori significance level acceptance was set at .05). If the absolute value of the standardized residual (SR) was greater than about 2.0, it was considered a noteworthy contributor to the significant chi-square value.\(^\text{16}\) Furthermore, negative standardized
residuals show observed counts were less than expected and positive values show observed counts were more than expected.

Further comparisons between the drug/gas treatments were not done because of incomplete datasets for most treatment arms.

Figures 11 and 12 are examples of several of the plots of initial pressures on tympanograms and display the down-sloping saline next to the erratic plots of the other medications in comparison to saline.

The pressure grade comparisons shown in Table 2 show that for most tests, the chi-square statistic was found to be significant ($P < .05$). The 3 chi-square tests that were not found to be significant included only 4 subjects and 22 comparisons. For all significant comparisons, an examination of their standardized residuals (SR) shows that the number of pressure grades that did not change was more than would be expected. For the acetylcysteine/O₂, the surfactant/air and the pseudoephedrine/O₂ treatments, less positive changes also occurred than were expected.
Subjective Difficulty (Holds)

There were only 4 of the 8 subjects with any holds during descent and only 20 subject-gas-drug conditions with holds among the 63 for which we have data. Thus, we have a very low incidence of holds among the divers in this study. Table 3 presents this data, but it would be difficult to obtain any definitive conclusions from these low numbers.

Table 3 displays the number of subjects who experienced holds in each of the gas-drug conditions described over the number of subjects exposed to the given gas-drug condition. (Holds/Attempted)

<table>
<thead>
<tr>
<th>Drug &amp; Gas</th>
<th>(-)</th>
<th>0</th>
<th>(+)</th>
<th>( \chi^2 )</th>
<th>P</th>
<th>( n_1/n_2/n_3 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxymetazoline &amp; Air</td>
<td>32%</td>
<td>55%</td>
<td>14%</td>
<td>5.54</td>
<td>0.07</td>
<td>4/9/22</td>
</tr>
<tr>
<td>Oxymetazoline &amp; ( O_2 )</td>
<td>22%</td>
<td>59%</td>
<td>20%</td>
<td>13.35</td>
<td>0.01</td>
<td>8/16/48</td>
</tr>
<tr>
<td>Acetylcysteine &amp; Air</td>
<td>27%</td>
<td>32%</td>
<td>41%</td>
<td>0.64</td>
<td>0.80</td>
<td>4/9/22</td>
</tr>
<tr>
<td>Acetylcysteine &amp; ( O_2 )</td>
<td>31%</td>
<td>64%</td>
<td>5%</td>
<td>22.43</td>
<td>&lt;0.001</td>
<td>7/14/42</td>
</tr>
<tr>
<td>Saline &amp; Air</td>
<td>30%</td>
<td>53%</td>
<td>17%</td>
<td>6.20</td>
<td>0.048</td>
<td>5/10/30</td>
</tr>
<tr>
<td>Saline &amp; ( O_2 )</td>
<td>20%</td>
<td>54%</td>
<td>26%</td>
<td>9.44</td>
<td>0.01</td>
<td>8/16/46</td>
</tr>
<tr>
<td>Surfactant &amp; Air</td>
<td>26%</td>
<td>62%</td>
<td>12%</td>
<td>13.47</td>
<td>0.001</td>
<td>6/12/34</td>
</tr>
<tr>
<td>Surfactant &amp; ( O_2 )</td>
<td>23%</td>
<td>56%</td>
<td>21%</td>
<td>11.38</td>
<td>0.004</td>
<td>8/16/48</td>
</tr>
<tr>
<td>Pseudoephedrine &amp; Air</td>
<td>50%</td>
<td>27%</td>
<td>23%</td>
<td>2.81</td>
<td>0.27</td>
<td>4/9/22</td>
</tr>
<tr>
<td>Pseudoephedrine &amp; ( O_2 )</td>
<td>19%</td>
<td>69%</td>
<td>13%</td>
<td>27.38</td>
<td>&lt;0.001</td>
<td>8/16/48</td>
</tr>
</tbody>
</table>

*Standardized residuals were only computed when \( \chi^2 \) statistic was found significant.
† Degrees of freedom = 2.
‡ Sample size for chi-squares is based on the on the number of pressure comparisons.
§ \( n_1 \) = subjects, \( n_2 \) = ears, \( n_3 \) = pressure grade comparisons.
DISCUSSION

The results show dramatic variability between subjects for each of the measures used to determine ETD as well as variability within a subject (inconsistencies noted between left and right ears). Results from each different assessment of ETD (ETOP versus NSI/DT versus subjective data) fail to provide any additional agreement.

The ETOP data revealed several interesting results. Firstly, ETOP measured both before and after diving while breathing oxygen was found to be much lower when compared to breathing air. This suggests that divers had an easier time equalizing their middle ear pressure overall before and after the oxygen dives than in the air dives. This is exactly the opposite of the anticipated result based upon both anecdotal/observational reports discussed earlier. This departure from expectations raises questions about the reliability of the ETOP test used and conclusions that can be drawn from ETOP data alone. Additionally, since all the pre-dive ETOP were performed in room air, the difference observed between pre-dive ETOP in air and oxygen conditions should be small. Pre-dive 1 should demonstrate no difference. This raises further questions with regard to variability in ETOP measurements and comparison of the post-dive results.

It is unclear why, when averaging pre-dives, mean ETOP across dives 1-3 measured before acetylcysteine was administered was significantly lower than other days when other drugs were administered. Since the trial was randomized and subject-blinded, there is no explanation as to why there would be a pre-dive effect on acetylcysteine. This may indicate that the morning after a dive, ET function was better than on the other medications. If this is a true beneficial effect, there was no significant benefit observed immediately following a dive other than when acetylcysteine was compared to saline.

When all dives are averaged, ETOP decreased significantly when oxymetazoline was administered. This may be another indicator of a beneficial effect. The decrease from pre-dive to post-dive ETOP suggests an improvement in ET function. However, this effect was only seen when all dives were averaged which includes diving on oxygen and air. In any one gas condition, the results were non-significant.

Two findings suggest a detrimental effect for acetylcysteine. For dive 1 alone, the post dive ETOP was significantly higher than the pre-dive ETOP, suggesting worsening. Along the same lines, the pre-dive 2 and 3 measures were higher (or worse) than pre-dive 1 for acetylcysteine, suggesting a progressive worsening over consecutive diving days.

Without a known benchmark, it is difficult to ascertain how much ETOP variability to expect across repeated measures in the absence of confounders; however it is clear that ETOP does vary greatly from subject to subject. There were several potential confounding factors identified that may have affected the observed results.

The first factor involves the subject pool evaluated. The data collected suggests significant variability in daily functioning of the ET. When combined with the small subject pool, this variability makes interpretation of the data difficult. Many more subjects or repeated dives are necessary in order to avoid problems presented by such wide variance in ET function. Despite
meeting model assumptions, small samples are vulnerable to even a single outlier that may lead to spurious conclusions. Secondly, the subjects evaluated were not necessarily the ideal population in which to test medications designed to improve ET function. Perhaps a more appropriate study group would be subjects who were unable to pass diving screening due to ETD or those who have problems equalizing middle ear pressure under normal conditions (eg, descent from altitude while flying.) These subjects would be much more likely to show a conclusive benefit from these medications rather than qualified divers who likely have highly functioning ETs by the nature of their occupation.

Another factor that may have provided significant variability is the administration of the medication via nasal inhaler. There were no attempts to verify that the medication reached the target area, namely, the ET. Perhaps the amount administered was not enough to completely coat the tube or it may only reach one ET to provide its limited effects there. Each subject may produce slight, unconscious changes each time the nasal inhaler was used. This would provide for inconsistent results even between days within subjects. The only way to confirm that medication is administered to the ETs equally and bilaterally would be with a nasopharyngeal optical scope.

The experimental design called for the use of nasal saline spray as the placebo, however saline may not be the ideal control condition. Divers do not typically use nasal saline prior to dives and, unless their mask is removed and they are inverted while they are submerged, copious amounts of saline do not typically wash down the nasopharynx before, during, or after a dive. The application of saline spray may have provided some unknown effect to the function of the ET during the study, but was originally intended for placebo and blinding purposes. A future study might consider using nothing as placebo, which would remove some of the blinding benefit, but would provide for more accurate comparison to current diving operations (the use of nothing prior to diving). Frequent saline flushing of the nasopharynx is sometimes recommended for recurrent sinusitis or congestion due to the ability of the solution to wash away mucus plugs and reduce local edema because of the relatively hypertonic solution. Thus, the saline spray may be producing a significant benefit that would make it inappropriate to compare it to the other medications as a placebo condition. Nasal saline may be considered as another drug condition to evaluate separately in a future study.

The results of each specific test also highlighted problems that occurred with each evaluation of ETD. While evaluating ETOP, certain individuals produced easily interpretable results (sharp vertical increase in the sound intensity with easily determined corresponding pressure levels) while others would report subjective clearing and the device would reveal no increase in sound intensity or would provide a very gradual increase making it difficult to identify the precise pressure at which ET opening occurs or if it occurred at all. There are some identified difficulties with sonotubometry that include the fact that not all ETs will open and function in the same manner. This may even change on a daily basis. For instance, even though the ET may open, it may not be significant enough to produce an easily identifiable change in the intensity of sound, thus leading to a false “failure to open” result. At times, the pressure associated with an intense Valsalva maneuver may transiently change the anatomy of the oropharynx that may cause a detectable change in the intensity of sound producing a false "positive opening" result. Another matter is that the air flow through the ET may create certain noises that can interfere with the tested frequencies. Better frequency selection would be an improvement, particularly far into the
ultrasonic range where physiologic sounds are scarcely produced. This also provides another source of variability in the experiment which makes interpretability with so few subjects difficult. Subjects that consistently provide equivocal results on sonotubometry could be excluded in favor of those who provide easily interpretable results on most days to enhance results. The number of subjects would have to be increased to allow for this selection criteria since a number of volunteers would be turned away based upon this. Along with these selection criteria, repeated baseline ETOP should be obtained over several days to establish a stable measure of function prior to any medications or diving. This would demonstrate baseline variability and identify those subjects who should be excluded because their ETOP is too difficult to objectively interpret.

Evaluating the subjective data, or number of holds, supports the suggestion that a different subject pool with more subjects would be necessary to prove effects. In this trial, at least two of the eight subjects were divers who were able to consciously open the ET with minimal effort; no increase in pressure in the nasopharyngeal space or swallowing was required. A total of four subjects had no difficulty clearing on any of the trials, thus providing only four subjects with any potential at all to show improvements on the number of holds. Most holds were noted in the air trials as that profile involved bounce dives to 60 feet whereas the oxygen dives were only to 15 feet. This problem could be addressed by increasing the number of subjects and specific subject selection criteria; specifically, selecting subjects with difficulty equalizing middle ear pressure.

Evaluation of the initial pressures on tympanometry did not produce the increasingly negative trend expected for consecutive days of diving in the saline condition. Without a consistent baseline to compare to, evaluation of the other drug effects is difficult. Only in 3 of the subjects was any consistently negative trend identified and when it was, it was often only in one ear with none of the drugs producing a consistent pattern of improving or reducing the difficulty clearing. The pressure grade analysis did not reveal any clear indication that any drug offered improved ET function. It is important to note that the tympanometry often took place first on most days, but sometimes took place after the sonotubometry. For consistency and reliable results, the tympanometry must take place first or the middle ear pressure could be equalized and the ET “prepared” for the NSI/DT. As mentioned above, it is well known that repeated opening of the ET makes successive attempts more effective.

Each analysis provides for different answers for determining which drug offers the most improvement in ET function. There is no evidence from this study that can clearly support one drug over the other. Oxymetazoline had the only significant positive change in the pre to post dive ETOP measurements. However, even this finding was significant only when all the measurements from 3 diving days and both oxygen and air breathing were averaged. This finding becomes non-significant for any given gas condition or diving day. Using the NSI/DT approach showed less positive influence than expected by chance in ET function with acetylcysteine and pseudoephedrine while breathing oxygen, and surfactant while breathing air.
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CONCLUSION

At this time, the results do not demonstrate a consistent beneficial effect of pseudoephedrine, surfactant, oxymetazoline, nasal saline, or acetylcysteine on the function of the ET. A study that employs more subjects may be able to provide more conclusive results. Likewise, a subject pool with more subjects who have difficulty equalizing their middle ear with ambient pressure will provide a better probability for demonstrating potential efficacy of the drugs on ET function. In the current study, only half of the eight subjects had any difficulty performing clearing maneuvers throughout the study. Repeated baseline ETOP would establish individual variability for comparison during the study.

The sonotubometry instrument used in this study exhibits great potential, but would benefit from further optimization and validation. Even when using other techniques to analyze ET function such as tympanograms, the results are highly variable. It seems that a methodology that can reproducibly measure ETOP is not currently available. Data can be collected to evaluate the ET, but current methods for measuring ET function are not sensitive or reliable enough to produce data that would allow for meaningful comparisons. Further evaluations should be delayed until more reliable techniques become available.

Another consideration would be whether the addition of simple nasal saline spray has any effect over no intervention in the function of the ET to ensure that the placebo condition is indeed “placebo.” Saline should probably be a “drug condition” in future studies with the control condition being the use of no medications, especially when considering the possible benefits of saline. This would impact blinding issues but may demonstrate that nasal saline has some benefit when compared to other drug conditions.

Perhaps more aggressive efforts to ensure delivery of the medication to the ET (nasopharyngeal fiber optic scope) would ensure that the medications consistently reach the ET, which may reduce variability in the subsequent ETOP data.

While the results of this study do not show any clear benefit of the medications, all of the medications tested theoretically have the potential to affect the ET. If the proper subject pool and a reliable ETOP measurement technique can be found, further study into these medications is warranted, given that a beneficial medication could result in significant dividends in the arenas of military screening, operational diving, aviation medicine, and clinical medicine.
REFERENCES

15. SPSS (for Windows) [computer program]. Release 15.0.0. Chicago, IL: SPSS Inc.; 2006.