# Tympanic membrane bleeding complications during hyperbaric oxygen treatment in patients with or without antiplatelet and anticoagulant drug treatment

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**Abstract**

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**Introduction:** Middle ear barotrauma (MEBt) is a frequently occurring complication of hyperbaric oxygen treatment (HBOT). High-grade MEBt may involve tympanic membrane (TM) haemorrhaging. Although many patients undergoing HBOT use antiplatelet or anticoagulant drugs, it is unknown whether these drugs increase the risk of MEBt and particularly TM bleeding complications.

**Methods:** This multicentre, prospective cohort study investigates the prevalence of MEBt and TM bleeding during HBOT in patients using antiplatelet/anticoagulant drugs, compared with control patients not on such medications. MEBt was assessed by video otoscopy of the TM pre and post HBOT and scored according to the modified Teed score. Any complications from previous HBOT sessions were retrospectively documented.

**Results:** Of 73 patients receiving HBOT, 34 used antiplatelet/anticoagulant drugs. Mild MEBt (Teed score 1 or 2) occurred in 23 of these 34 patients and in 31 of the 39 controls. Teed score 3 MEBt occurred in only two of the control-group patients and none of the patients using antiplatelet/anticoagulant drugs. Two patients using anticoagulant drugs reported epistaxis during a previous HBOT session; epistaxis was not reported by any control patients.

**Conclusion:** Low-grade MEBt is common during HBOT; however, high-grade barotrauma is rare with current chamber operating procedures. Patients using antiplatelet/anticoagulant drugs potentially may be prone to MEBt-associated haemorrhagic complications, but we did not observe any such increase in this cohort. Only mild epistaxis occurred in patients using anticoagulant drugs.

**Key words**

Middle ear; barotrauma; hyperbaric oxygen therapy; medication; cardiovascular; haematology; risk factors

## Introduction

There are various well-established indications for the use of hyperbaric oxygen treatment (HBOT).[1] Although generally a safe procedure, the most prevalent adverse event associated with HBOT is middle ear barotrauma (MEBt).[2] Many indications for HBOT relate to macro- and/or microvascular ischaemic injury, such as non-healing skin ulcers. In these patients with vascular disease, the use of prophylactic antiplatelet or anticoagulant medication is common. It is possible that individuals using antiplatelet/anticoagulant drugs are at increased risk of developing bleeding complications during hyperbaric exposure. In cases of MEBt, the mucosal lining is distended and blood vessels may rupture, possibly leading to haemotympanum and tympanic membrane (TM) rupture causing pain, hearing loss, and anxiety.[3]

There are no data on the influence of the use of antiplatelet/anticoagulant drugs on the prevalence of bleeding complications from MEBt during HBOT. In the present study, otological effects of hyperbaric exposure were assessed in patients undergoing HBOT and using antiplatelet/anticoagulant medication compared with control patients not using such medication.

## Methods

### STUDY DESIGN

This prospective, multicentre, observational cohort study included 73 patients from four hyperbaric centres in the Netherlands. The study protocol was approved by the Medical Ethical Committee of the Amsterdam Medical Center (approval W13_079 # 13.17.0099). A sample size of 30 patients per group was calculated to detect a substantial increase in the incidence of MEBt (Teed grade ≥ 3, see below) to 20% or more from an estimated 4% in controls with 80% power and an α-level of 5% using one-sided testing and accounting for 20% loss to follow-up.

A total of 93 consecutive patients treated with HBOT were evaluated of whom 73 met the inclusion/exclusion criteria. All participants provided written informed consent. All participants had to have been previously evaluated and found fit for HBOT by their hyperbaric physician. During this evaluation, routine otoscopy was performed to exclude pre-existing pathology. All patients were informed about HBOT and had been taught various middle ear equalizing manoeuvres.

For the present study, individuals were excluded in case of incomplete video-otoscopic examination during pre- and/or post-treatment evaluation, defined as the inability to assess > 50% of the tympanic membrane (TM) on the digital image. Exclusions occurred mostly due to the presence of cerumen that could not be immediately removed. For the final analysis, 34 participants using antiplatelet/anticoagulant drugs were compared with 39 control patients not using antiplatelet/anticoagulant drugs, thus meeting the predetermined sample size to reach sufficient statistical power.

### VIDEO OTOSCOPY AND MEBt GRADING

Bilateral video otoscopy was performed before and within 15 min after a HBOT session. In all participants, otoscopy was carried out by a trained staff member using a Welch Allyn™ Digital Macroview Otoscope 719 series. Both TMs of each patient were examined and photographed before and after HBOT. Photographs were blinded and independently assessed by two investigators (RAvH and VAF) for grading MEBt according to the modified Teed classification:[4]

Grade 0 – Symptoms without signs;
Grade 1 – Injection of TM, especially along the handle of the malleus;
Grade 2 – Injection plus slight haemorrhage within the substance of the TM;
Grade 3 – Gross haemorrhage within the substance of the TM;
Grade 4 – Free blood in the middle ear, as evidenced by blueness and bulging;
Grade 5 – Perforation of the TM.

Photographs were taken in the standard mode with a resolution of 1280 x 1024 megapixels in jpg format. A Teed score of ≥ 3 was considered to be a significant MEBt.

### QUESTIONNAIRE

Patients were asked to complete a 10-min questionnaire in which treatment indication, comorbid diseases, ENT disorders, medication use and bleeding symptoms were evaluated. The questionnaires enquired about bleeding symptoms, both in daily life and in relation to any of their previous HBOT sessions. For quantification of the general occurrence of bleeding symptoms unrelated to HBOT (e.g., the occurrence of spontaneous bruising and epistaxis, etc), the ISTH/Tosetto bleeding score was used in a slightly abbreviated form.[5,6] This score ranges from 0 (no symptoms) to 22 points, and is widely used to characterize bleeding propensity; however, it was developed to diagnose congenital bleeding disorders and has not been specifically validated to investigate the haemorrhagic effects of antiplatelet or anticoagulant drugs.

### HBOT PROTOCOL

All HBOT was done in multiplace chambers with audio and camera observation. During most sessions, a trained staff member was physically present inside the chamber to assist patients when required. In the case of any patient indicating difficulty clearing their ears, compression was immediately interrupted. Compression rates ranged from 1.0–1.5 metres' sea water (msw) equivalent depth per minute for a total of 10–15 min to reach the treatment pressure of 14–15 msw (approximately 243 kPa). Patients received three intervals of HBOT of 20–30 min each with a 5–10 min break between each session. The chamber was decompressed at a rate of 1.0–1.5 msw·min$^{-1}$. The total treatment duration ranged from 100–130 min.

### STATISTICAL ANALYSIS

Data are presented as the number of patients (*n*), mean or median (range) where appropriate. Analyses were performed with SPSS version 21. The primary research question regarding the proportion of MEBt in participants using antiplatelet/anticoagulant drugs vs. controls was tested with the Chi-square test. For secondary analyses, normality of the quantitative variables was checked with the Shapiro-Wilk test. Normally distributed continuous variables were compared with a Student's *t*-test. Non-normally distributed numerical variables were analysed with the Kruskall-Wallis test, and nominal and ordinal variables were analysed with the Chi-square test. Fisher's exact test was used when expected cell counts were low and comprised ≥ 25% of a table. The *P*-value was one-tailed for the primary research question investigating whether there would be an increase in tympanic bleeding complications associated with the use of antiplatelet/anticoagulant drugs; for other statistical comparisons, *P*-values were calculated based on a two-tailed level of significance defined at 0.05.

## Results

### BASELINE CHARACTERISTICS

Of the 73 patients included in the study, 34 used antiplatelet or anticoagulant drugs. The types of antiplatelet/anticoagulant drugs used were acetylsalicylic acid (*n* = 26), vitamin K antagonists (*n* = 7), dipyridamole (*n* = 3), clopidogrel (*n* = 2), low-molecular-weight heparin (*n* = 1) and, in some patients, a combination of these (*n* = 6).

Table 1 presents the baseline characteristics of the two study groups. As expected, the Tosetto bleeding score was higher in participants using antiplatelet/anticoagulant drugs, reflecting a noticeably higher bleeding tendency in daily life. Patients using these agents were more often male and had a higher average age, probably owing to the higher incidence of cardiovascular disease in males of increasing age. One patient using antiplatelet drugs and one control patient reported having experienced a MEBt with TM haemorrhage during a HBOT session prior to participating in the present study. Two patients using anticoagulant drugs, but none of the controls, reported having experienced epistaxis during a previous HBOT sessions.

**Table 1**
Characteristics of the study patients, AP/AC - antiplatelet/anticoagulant; NA - not available

| | AP/AC patients ($n$ = 34) | Controls ($n$ = 39) |
|---|---|---|
| Sex (M/F) | 25/9 | 19/20 |
| Age (y; mean, range) | 64 (34–82) | 58 (29–77) |
| HBO sessions (median, range) | 20 (0–152) | 18 (0–44) |
| Tosetto bleeding score ($n$) | | |
| 0–3 | 20 | 29 |
| 4–5 | 8 | 8 |
| ≥ 6 | 4 | 2 |
| NA | 2 | 0 |
| Bleeding incidents during previous HBOT | | |
| Yes | 3 | 1 |
| No | 29 | 38 |
| NA | 2 | 0 |

A clinically significant proportion of the patients (55 of 73) had signs of MEBt from the previous HBOT sessions (Table 2). One control patient had a TM injury (Teed score 3) from the HBO treatments prior to participating in our study sessions. The median number of previous sessions was 28 (range 0–157) in the patients using antiplatelet/anticoagulant drugs versus 19 (range 0–44) in controls. A maximum of 40 sessions is provided per HBOT cycle, whereupon in exceptional cases a repeat cycle may be provided after at least a three-month interval.

MEBt POST HBOT

In the control group, two of 71 TMs satisfactorily visualized in the 39 patients had a Teed score of ≥ 3, whilst none of 66 TMs from the 34 antiplatelet/anticoagulant patients had a Teed score > 2. There was no observed increase in haemorrhagic TM complications during HBOT in either group (Table 2). Six patients in the control group and seven in the antiplatelet/anticoagulant group showed a higher Teed score post HBOT than pre HBOT in one or both TMs. A history of aural symptoms during HBOT was associated with a higher Teed score after the treatment. There was no association of Teed scores with age or sex or the number of previous HBOT sessions. The two patients experiencing a Teed grade 3 MEBt were on their ninth and tenth sessions respectively.

Also, no non-MEBt-related bleeding complications, such as epistaxis or sinus squeeze, occurred during the study sessions.

## Discussion

The present study confirms previous reports that mild forms of MEBt (modified Teed grades 1 and 2) occur frequently during HBOT.[7–9] For example, in a study evaluating the efficacy of topical decongestants on MEBt in HBOT, approximately 45% of patients had a Teed score greater than zero.[8] In another study, 17% of 782 HBOT patients reported clinically apparent middle ear symptoms consistent with MEBt occurrence.[2] Of note, the incidence of MEBt reported here is based on TM assessment, irrespective of the presence of MEBt symptoms. Patients who are unable to auto-inflate the middle ear, or who have positive pathological findings on otoscopy, are considered to be at higher risk to develop MEBt, with a reported incidence of MEBt ranging from 37 to 94%.[10–12] For this reason, as part of standard care at our hyperbaric facilities, all patients are extensively assessed for ENT comorbidity prior to the initiation of HBOT, and receive detailed instructions about middle ear equalization. The incidence of MEBt may depend on the compression rate, with a slow rate resulting in a significantly lower incidence of MEBt in one study.[13] In the present study, a slow compression rate of 1.0–1.5 msw·min$^{-1}$ was used, which may explain the low incidence of serious MEBt.

This is the first study specifically designed to investigate the occurrence of TM haemorrhage in patients using antiplatelet or anticoagulant medication undergoing HBOT. Although bleeding phenomena during daily life occur more frequently in individuals using these agents, we found no evidence in our study that TM bleeding complications are increased in such patients. This is of importance, since aggravation of MEBt sequelae by TM haemorrhaging could cause anxiety and/or panic during the HBOT session and create a risk for aggravated middle ear injury.

The occurrence of epistaxis reported by two patients during one of their previous HBOT sessions, suggests that epistaxis might be a recurrent symptom in patients using anticoagulant drugs and undergoing HBOT. The epistaxis that occurred was easily managed by application of local pressure and, therefore, represented only a minor complication.

In a recent study investigating risk factors for MEBt with the aim of identifing patients requiring tympanostomy tubes, the use of anticoagulant therapy correlated with the incidence of MEBt in the bivariate, but not in the multivariate analysis.[8] However, because that study was not designed to investigate the influence of anticoagulant drugs, few details were provided.

The present study has several limitations. The investigation included patients who had undergone a substantial number of previous HBOT sessions and, generally, had signs of MEBt prior to the studied HBOT session. However, as no patient had a Teed score of ≥ 3, we believe that this did not affect our primary research question. Also, by including a baseline analysis, we were able to differentiate between pre-existing and new tympanic aberrancies. However, we cannot exclude that patients who were intolerant of HBOT, possibly owing to MEBt occurrence, had previously stopped their HBOT

**Table 2**
TEED scores for MEBt before and after the HBOT study session; Teed scores, ranging from 0 to 5, with number of subjects before session and immediately after the session. The highest Teed score from right and left tympanic membranes from each subject was used to calculate this table; there were no statisically signifcant difference between the two groups

| | Patients using AP/AC drugs ($n$ = 34) | | Control patients ($n$ = 39) | |
|---|---|---|---|---|
| **Teed score** | **Before** | **After** | **Before** | **After** |
| 0 | 10 | 9 | 8 | 8 |
| 1 | 19 | 18 | 20 | 15 |
| 2 | 5 | 7 | 10 | 14 |
| 3 | 0 | 0 | 1 | 2 |
| 4/5 | 0 | 0 | 0 | 0 |

and this might have led to some selection bias. Also, we powered the study to compare any patient using any type of antiplatelet/anticoagulant drug with a control group not using these drugs. However, there may be differences between the adverse effects of the various individual subtypes of drugs or combinations thereof. The present study was underpowered to allow any meaningful sub-group analyses for different medications. Our study was too small to detect rare, but possibly more severe, complications from the use of antiplatelet/anticoagulant drugs.

## Conclusions

Mild (modified Teed score 1 to 2) MEBt was common in our patients. We found no evidence that TM bleeding complications from HBOT were increased in subjects using antiplatelet/anticoagulant drugs. Therefore, these drugs should not be considered to be a contraindication to HBOT. However, every effort should be made to prevent MEBt in all patients undergoing HBOT.

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