# Short communication

## Validation of sham treatment in hyperbaric medicine: a randomised trial

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**Abstract**
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**Introduction:** This study aimed to determine the lowest possible atmospheric pressure in the 111–152 kPa (1.1–1.5 atmospheres absolute [atm abs]) range that would require the patients to equalise their ears, allowing an effective sham for a 203 kPa (2.0 atm abs) hyperbaric exposure.
**Methods:** We performed a randomised controlled study on 60 volunteers divided into 3 groups (compression to 111, 132 and 152 kPa (1.1, 1.3, 1.5 atm abs) to determine the minimum pressure to obtain blinding. Secondly, we applied additional blinding strategies (faster compression with ventilation during the fictitious compression time, heating at compression, cooling at decompression) on 25 new volunteers in order to enhance blinding.
**Results:** The number of participants who did not believe they had been compressed to 203 kPa was significantly higher in the 111 kPa compressed arm than in the other two arms (11/18 vs 5/19 and 4/18 respectively; $P = 0.049$ and $P = 0.041$, Fisher's exact test). There was no difference between compressions to 132 and 152 kPa. By applying additional blinding strategies, the number of participants who believed they had been compressed to 203 kPa increased to 86.5 %.
**Conclusions:** A compression to 132 kPa, (1.3 atm abs, 3 metres of seawater equivalent) combined with the additional blinding strategies of forced ventilation, enclosure heating and compression in five minutes, simulates a therapeutic compression table and can be used as a hyperbaric placebo.

### Introduction

In hyperbaric medicine, the recommended therapeutic indications are regularly criticised due to a lack of high-level evidence, as well as the limited number of randomised trials. A sham procedure can be defined as one performed on a control group participant to ensure that he or she experiences the same incidental effects of the procedure as do those participants on whom a true procedure is performed. Randomised trials which do not include a sham control group may be at risk of bias due to a placebo effect. The addition of a sham group (i.e., a placebo control group) allowing patient-blinding can improve the quality of evidence.

Conducting a sham control treatment in hyperbaric medicine is particularly challenging as increased atmospheric pressure is often easily perceived by patients who need to equalise their ears. Conversely, an absence of increased pressure may also be easily identified by patients in the sham control group who will not need to equalise their ears. In hyperbaric medicine one challenge in conducting a sham treatment is to determine the lowest atmospheric pressure that still requires patients to equalise their ears, (allowing blinding) whilst minimising the biological effect of that pressure.

A recent systematic review of 42 studies involving placebo groups in hyperbaric medicine identified three types of strategies for conducting a sham: shallow air compressions to 111–152 kPa (1.1–1.5 atmospheres absolute [atm abs]) breathing 21% oxygen; equivalent depth compressions to 203–253 kPa (2.0–2.5 atm abs) breathing a gas mixture adjusted to deliver an inspired $PO_2$ similar to air at 101.3 kPa (1.0 atm abs); or equivalent depth compressions to 203–253 kPa (2.0–2.5 atm abs) breathing 21% oxygen.[1] A risk/benefit analysis favoured shallow air compressions (1.1–1.5 ATA) breathing 21% oxygen. This would allow acceptable blinding at a very low level of risk whilst minimising the risk of a biological effect from the minimally increased inspired $PO_2$. However, the optimal pressure for a sham treatment within the 111–152 kPa range remained undetermined.

In order to guide hyperbaric medicine researchers in conducting sham treatments, this study aimed to determine the lowest possible atmospheric pressure in the 111–152 kPa range that would include a requirement for patients to equalise their ears, allowing an adequate sham for treatments conducted at 203–253 kPa.

## Methods

### ETHICS APPROVAL AND PARTICIPANTS

Application was made to our institutional ethics board '*Commission Cantonale d'Ethique de la Recherche*' (Req-2018-00387) and the study was exempted from comprehensive ethical review. Each volunteer was given a detailed participant information sheet which explained what would take place during the session, and gave written informed consent. Participants were volunteer healthcare professionals from the University Hospital of Geneva, Switzerland recruited through information published on the hospital's intranet site. All were evaluated by a hyperbaric physician to exclude any contraindication.

### DESIGN, INTERVENTION AND OUTCOME MEASURES

The study was carried out in two stages.

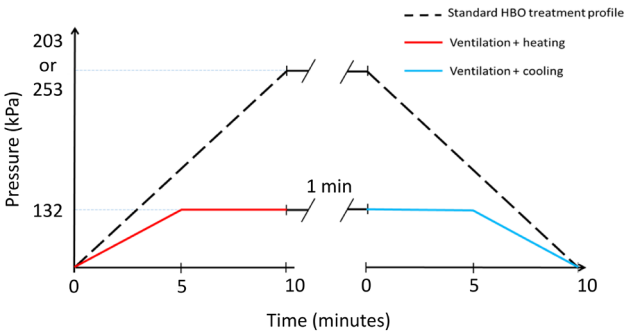
In Stage 1, we conducted a randomised trial, using a 1:1:1 ratio and block size of six. Volunteers were randomised to three pressure profiles: Group A, 111 kPa (1.1 atm abs, 1 metre sea water [msw] equivalent); Group B, 132 kPa (1.3 atm abs, 3 msw); Group C, 152 kPa (1.5 atm abs, 5 msw). Randomisation was performed using the RAND function in Excel. All three groups had identical diving sequences; pressurisation over 10 minutes, duration at pressure for one minute, and decompression over 10 minutes.

For Stage 2, a new cohort of 25 participants was recruited. All were compressed to 132 kPa (1.3 atm abs, 3 msw) and we decreased the compression time from 10 minutes to five minutes to increase the sensation of pressure change to a rate closer to that experienced during a normal treatment and thus improve blinding. Additionally, forced ventilation using air addition accompanied by simultaneous air exhaust (sometimes referred to as 'flushing') more closely replicated the noise of a normal treatment during compression. To mimic the patients' usual experience of heat during compression and cold during decompression, we used the hyperbaric chamber's air conditioning system to heat during the sham compression, and during decompression both forced ventilation and cooling of the chamber was performed (Figure 1).

Each participant was compressed separately in the department's hyperbaric multi-place chamber (HAUX-STARMED 2400/4/SC3) and accompanied (with the exception of volunteers from the hyperbaric department) by a hyperbaric nurse.

Immediately after the decompression, participants were asked to indicate whether or not they believed they had been compressed to an equivalent depth of 10 msw (203 kPa, 2.0 atm abs). This pressure was chosen as the purpose of this study was to validate a sham for a planned double-blinded, randomised controlled trial on the effects of hyperbaric oxygen treatment (HBOT) during sickle cell crisis. In this planned trial, the patients in the treatment arm will be treated using an adapted exposure at 203 kPa (2.0 atm abs) (Clinical Trials: NCT05289700). Our primary outcome was, therefore, to measure participants' blinding perception after decompression, defined as their belief that they had been compressed to 10 msw equivalent during the session.

**Figure 1**
Table profile with additional blinding strategies; compression over five minutes with forced ventilation ('flushing') for 10 minutes (theoretical duration of compression), heating during compression and cooling during decompression




The participant information sheet contained the following information:

"*You are going to participate in a study aimed at validating a placebo group in hyperbaric conditions.*
*You will enter the chamber accompanied by a nurse. You will or will not undergo compression at 10 meters depth following a standard profile including:*
*– Pressurisation for 10 minutes. During this phase you may feel a sensation of heat and noise (gas compression). You will also need to balance your ears by performing a so-called Valsalva manoeuvre or by swallowing. These manoeuvres are close together at first, then more and more distant.*
*– A stay at the bottom reduced to a few minutes. Normally this phase lasts 65 minutes.*
*– A descent lasting 10 minutes. During this phase you may feel a sensation of cold and noise (gas decompression). No balancing manoeuvres are required. These are done on their own.*"

On completion of the hyperbaric compression and decompression participants were asked to answer four questions with an answer chosen from (yes/no/I can't tell):

1. Do you think you have undergone compression as explained to you (compressed to 10 msw)?
2. Did you need to balance your ears?
3. Did you feel hot on compression?
4. Did you feel cold on decompression?

**Table 1**
Participant characteristics; F – female; IQR – interquartile range; M – male

| Parameter | Group A (111 kPa) | Group B (132 kPa) | Group C (152 kPa) |
|---|---|---|---|
| Sex ratio (M/F) | 16/4 | 12/8 | 13/7 |
| Age (years) Median [IQR] | 32.5 [27.7;43.0] | 32.0 [27.5;38.7] | 36.0 [30.7;44.2] |
| Relevant experience: None/Diver/Hyperbaric medicine attendant | 9/4/7 | 10/4/6 | 9/4/7 |

**Table 2**
Response to the question "*have you been compressed to 10 metres*?" with participants stratified according to diving or hyperbaric experience; ? – participants who responded "*I can't tell*"

| Relevant experience | Group A (111 kPa) | | | Group B (132 kPa) | | | Group C (152 kPa) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Yes | No | ? | Yes | No | ? | Yes | No | ? |
| None | 5 | 4 | 0 | 7 | 3 | 0 | 8 | 0 | 1 |
| Diver | 0 | 3 | 1 | 2 | 1 | 1 | 2 | 2 | 0 |
| Hyperbaric attendant | 2 | 4 | 1 | 6 | 1 | 0 | 4 | 2 | 1 |
| Total | 7 | 11 | 2 | 14 | 5 | 1 | 14 | 4 | 2 |

**Table 3**
Responses from the 25 new volunteers with no diving experience in Stage 2; ? – participants who responded "*I can't tell*"

| Question | Yes | No | ? |
|---|---|---|---|
| Do you think you have undergone compression as explained to you? | 22 | 1 | 2 |
| Did you need to balance your ears? | 25 | 0 | 0 |
| Did you feel hot on compression? | 5 | 20 | 0 |
| Did you get cold on decompression? | 22 | 3 | 0 |

## SAMPLE SIZE AND ANALYSIS

For Stage 1 we elected to recruit a convenient sample size of 60 total, i.e., 20 participants per group. Based on our primary outcome, a sample of 60 participants for three groups, and assuming a power of 0.8 and alpha risk of 0.05 (two-tailed), an effect size of 0.4 could be detected.

All participants who responded "*I can't tell*" were excluded as their response were not helpful in answering our research question. Our binary primary outcome was analysed using a Fisher's exact test, comparing B and C groups to A group. A two-tailed $P$-value of $< 0.05$ was considered significant for all analyses. Statistical analysis was performed using SPSS 16.0 (SPSS, Chicago, IL).

## Results

In Stage 1 sixty volunteers were recruited and included in the analysis, i.e., 20 in each group. Relevant demographics are shown in Table 1. The number of participants responding "*No, I was not compressed to 10 msw*" was significantly higher in the 111 kPa group than in the 132 and 152 kPa groups (11/18 vs 5/19 and 4/18 respectively; $P = 0.049$ and $P = 0.041$). There was no significant difference in responses between participants compressed to 132 kPa (3 msw) or 152 kPa (5 msw) ($P = 1$). We note that the 111 kPa group had a higher proportion of males than in the 132 or 152 kPa groups (4:1 vs 1.5:1 or 2:1). Diving/hyperbaric attendant experience did not appear to dramatically impact perception of pressurisation, particularly in the 132 and 152 kPa exposures although numbers are small (Table 2).

In the second stage, a further twenty-five new volunteers without hyperbaric experience were included. All were compressed to 132 kPa (1.3 atm abs, 3 msw equivalent). The number of participants who believed they had been compressed to 203 kPa (2.0 atm abs, 10 msw) increased to 22/25 (88%) with one who believed they were not, and two who couldn't tell. One hundred percent of volunteers reported equalising their ears (Table 3). One volunteer described ear pain without it being necessary to interrupt the session. An examination post session, showed a grade one barotrauma.

## Discussion

In order to initiate randomised, double-blinded, placebo-controlled trials in hyperbaric medicine, we evaluated the shallow compression profile that best simulated a therapeutic table. Although compression to an equivalent pressure such as 203 or 253 kPa (2.0 or 2.5 atm abs) creates strong conditions for blinding, as concluded by others,[1] we believed that a lower pressure compression was simpler and ethically acceptable.[1]

We hypothesised that a lower pressure compression could give the patient the impression that they participated in a true HBOT treatment at 203 or 253 kPa (2.0 or 2.5 atm abs). By testing several pressures we were able to identify the lowest pressure that seemed adequate for effective blinding. Compression to 111 kPa (1.1 atm abs, 1 msw equivalent) in 10 minutes did not appear to create sufficient blinding. There was no difference in blinding success between a compression to 132 vs 152 kPa (1.3 atm abs, 3 msw vs 1.5 atm abs, 5 msw) and blinding seemed acceptable. Although the group with a low degree of blinding had a much higher proportion of males, this difference seems an implausible explanation for the poor blinding success. Blinding was further improved by reducing the compression and decompression time to five minutes while maintaining forced ventilation for 10 minutes and using additional blinding strategies such as the addition of heat to compression and cold to decompression. On the second set of volunteers, blinding was almost total with only one participant claiming not to have been compressed while all claimed to have balanced their ears.

The inspired $PO_2$ breathing air at a pressure of 132 kPa (1.3 atm abs) is equivalent to breathing 28% oxygen at 101.3 kPa (1.0 atm abs). Even if this small rise in inspired $PO_2$ does not correspond to a totally inert placebo, it should not have a significant impact on results of most trials of true HBOT.

## Conclusion

A compression to 132 kPa (1.3 atm abs, 3 msw equivalent) in conjunction with confounding elements such as forced ventilation, enclosure heating and compression over five minutes, simulates a therapeutic compression table and can be used as a hyperbaric sham. This profile has the advantage of being extremely low risk and with an inspired $PO_2$ equivalent to 28% oxygen at atmospheric pressure, there can be no oxygen effect that would require hyperbaric exposure to achieve.

## References

1 Lansdorp CA, van Hulst RA. Double-blind trials in hyperbaric medicine: A narrative review on past experiences and considerations in designing sham hyperbaric treatment. Clin Trials. 2018;15(5):462–76. doi: 10.1177/1740774518776952. PMID: 29865904. PMCID: PMC6136075.

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