Effect of caffeine consumption on tissue oxygen levels during hyperbaric oxygen treatment

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Stephens M, Frey M, Mohler S, Khamis H, Penne R, Bishop J, Bowden A. Effect of caffeine consumption on tissue oxygen levels during hyperbaric oxygen treatment. Undersea Hyper Med 1999; 26(2):93–97. — Ten men were exposed to hyperbaric oxygen (HBO₂), and their tissue oxygen levels were monitored after they drank either placebo or caffeine beverages. Transcutaneous tissue oxygen (Ptco₂) monitor measurements in a normobaric air environment were initially obtained from transducers on the subject’s chest and foot. The subjects then consumed either the caffeine (3 mg · kg⁻¹) or the placebo beverage, and after 20 min the subjects were pressurized in a hyperbaric chamber to 2.36 atm abs (1 atm = 101.3250 kPa). The test subjects began breathing 100% oxygen at 2.36 atm abs, 30 min after administration of the experimental beverage, and continued for 30 min, after which the final chest and foot Ptco₂ measurements were recorded (1 h after ingestion of the test drink). Each subject underwent a second hyperbaric exposure during which the alternate drink was administered (either the placebo or the caffeine), and Ptco₂ measurements were again obtained. The increase in right foot Ptco₂ values during HBO₂ exposure was significantly smaller after caffeine consumption than after placebo (P = 0.0018).

caffeine, hyperbaric oxygen, tissue oxygen levels

Orally consumed caffeine may produce peripheral vasoconstriction in humans, which causes decreased peripheral blood flow and may lead to a decrease in tissue oxygenation (1–6). Furthermore, there is an association between tissue hypoxia, as measured by transcutaneous oxygen (Ptco₂) monitor electrode and impaired wound healing (7–12). Also, hyperbaric oxygen (HBO₂) exposure may be therapeutic in nonhealing hypoxic wounds (13,14). However, there is concern that orally consumed caffeine, because of its peripheral vasoconstrictive effect, could have an adverse impact on the therapeutic effect of HBO₂ for problem wounds. It is not known whether caffeine consumption affects the ability of HBO₂ treatment to increase tissue oxygen levels. The purpose of this study was to determine if the ingestion of caffeine will significantly affect the elevation in tissue O₂ levels in the lower extremities of normal human subjects caused by a HBO₂ environment. We used Ptco₂ electrodes to monitor the subjects because it has been demonstrated that Ptco₂ measurements accurately reflect peripheral tissue oxygen levels in humans (15).

METHODS

This study was conducted at Wright-Patterson Air Force Base, Department of Hyperbaric Medicine, Dayton, Ohio, using their large, multiplace treatment chamber.

Subjects: Ten men between the ages of 24 and 58 yr (mean 39.2 yr, SD 7.8) participated. They were chosen from among the hyperbaric chamber certified technicians at Wright-Patterson Air Force Base; all were Air Force health care workers. The subjects were limited to males because there was not a sufficient number of female chamber-qualified subjects available. All subjects were screened for clinically significant illness and all had official Air Force medical clearance for hyperbaric duty; there were no significant risks above and beyond usual occupational exposure levels for the subjects. A total of 12 subjects were initially selected but 2 subjects were excluded from the study based on pre-established exclusionary criteria (one because of concurrent antihistamine use for acute sinusitis and another due to caffeine use less than 12 h before the study dive). Table 1 is a summary of pertinent subject descriptive data.

Exclusion criteria included use of medications during the study period, clinically significant physical anomaly of a subject’s right leg, development of acute illness during the study period, preexistence of significant chronic illness, age less than 18 yr or greater than 65 yr, caffeine use less than 12 h before any dive, oral intake (except water) less than 6 h before any dive, and decision of the subject to voluntarily withdraw from participation in the study for any reason.

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Table 1: Summary of Subject Descriptive Data

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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<tbody>
<tr>
<td>Total number:</td>
<td>10</td>
</tr>
<tr>
<td>Gender:</td>
<td>male</td>
</tr>
<tr>
<td>Age, yr:</td>
<td>24–58 (mean 39.2, SD 7.8)</td>
</tr>
<tr>
<td>Weight, lb:</td>
<td>135–204 (mean 144, SD 36.7)</td>
</tr>
<tr>
<td>Height, in:</td>
<td>64–74 (mean 69.25, SD 3.3)</td>
</tr>
<tr>
<td>Aerobic conditioning:</td>
<td>7 excellent; 3 average</td>
</tr>
<tr>
<td>(defined objectively by subjects)</td>
<td></td>
</tr>
<tr>
<td>Caffeine use:</td>
<td>4 regularly; 3 occasionally; 3 rarely</td>
</tr>
<tr>
<td>Tobacco use:</td>
<td>1 rarely; 9 never</td>
</tr>
<tr>
<td>Previous hyperbaric experience:</td>
<td>yes</td>
</tr>
<tr>
<td>Last caffeine use (before test dive):</td>
<td>all &gt;12 h</td>
</tr>
<tr>
<td>Last meal (before test dive):</td>
<td>all &gt;6 h</td>
</tr>
<tr>
<td>Current health status:</td>
<td>all healthy</td>
</tr>
<tr>
<td>Current medications:</td>
<td>none</td>
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</table>

Routine use of tobacco or caffeine was not included in the exclusion criteria.

Subject participation was voluntary, and appropriate informed consent regarding risks, benefits, and the voluntary nature of continued participation as subjects was obtained. The study protocol was reviewed and approved by the human use and research committees of both Wright State University and Wright-Patterson Air Force Base Medical Center. Medical monitoring was performed by the Flight Medicine Department located adjacent to the Hyperbaric Medicine Department at Wright-Patterson Air Force Base Medical Center. Medical and disability insurance for the subjects was provided under their standard Air Force health care policies.

Tissue oxygen monitors: Tissue oxygen pressures were measured using the Radiometer TCM3 Ptco₂ monitor, which has been shown to be accurate in the measurement of tissue O₂ levels for both the normobaric and hyperbaric environment (7–12). Also, O₂ levels measured by Ptco₂ correlate with peripheral blood flow in hemodynamically stable patients (7–12). Each subject was fitted with a Ptco₂ monitor electrode on the dorsum of the right foot (soft tissue between the first and second metatarsal bones 2 cm from the distal head of the first metatarsal) and an electrode on the chest (left midclavicular line, second intercostal space). The right foot was used because the distal extremities are generally the sites where problem wounds occur (15), and the right foot is the extremity most distal to the heart. The chest electrode served as a reference site most closely reflecting the central arterial oxygen level (12).

The same monitor and electrode ensemble was used for each experiment, except that the electrode’s semi-permeable membrane was replaced with a new membrane before each experiment. Care was taken to avoid placing monitor electrodes over bone, hair, or callused skin because of possible error in Ptco₂ measurements due to a diminution of the O₂ gradient through these tissues. The electrodes were protected from cool drafts (such as from air-conditioning vents) because this could lead to measurement error; the electrode sites were covered by a light blanket. To further control for movement and positional-induced experimental error, the subjects lay quietly on a gurney with 45° head up angle (from the waist) and with legs extended horizontally for the duration of each experiment.

Experimental protocol: At the start of each experiment, baseline Ptco₂ measurements were obtained from the chest and foot leads while the subject was breathing room air at 1 atm in the chamber. The subjects were then administered either the caffeine or the placebo beverage. Twenty minutes after the start of the experiment the chamber was pressurized to 2.36 atm over 10 min with the subject remaining inside the chamber but continuing to breath air. After pressurization of the chamber, and 30 min after ingestion of the experimental beverage, the test subjects began breathing 100% O₂ continuously from oxygen hoods. The final chest and foot Ptco₂ measurements were recorded after 30 min of breathing 100% O₂ at 2.36 atm abs chamber pressure (final measurements being obtained 1 h after ingestion of the experimental drink and with subjects still breathing 100% O₂ at 2.36 atm abs). The chamber was then depressurized marking the end of the experiment.

The chamber was pressurized using a normal air atmosphere, with the same operational and safety protocols used for standard treatment. The chamber temperature was maintained at 79°F (adjusted as required for occupant comfort). Ascent and descent rates were 5 ft · min⁻¹ and 7 ft · min⁻¹, respectively, with stops as required for subject comfort, safety, medical, or technical reasons.

In each experiment the subject was administered either a dose of caffeine or a placebo. The dose of caffeine was 3 mg · kg⁻¹ (caffeine citrate solution, 10 mg · ml⁻¹, sweetened with artificial sweetener), diluted with distilled water to a volume of 100 ml. The placebo was an equal quantity of artificially colored and sweetened water. Both drinks were warmed to 100°F. The dosages of caffeine were chosen so as to approximate the concentration of caffeine in caffeinated coffee (approximately 150 mg caffeine per cup of coffee), with the warm liquid format serving to approximate the absorption profile of coffee (16). Both the placebo and the caffeine test drinks were consumed by the subjects from Styrofoam cups; both liquids were similar in appearance and taste; the entire drink was consumed in no more than 1 min.

Random administration of the caffeine and placebo beverages was assured by assigning each subject a numerical designator, corresponding with the order of their entry.
into the study, and then pairing subjects according to a scheme generated using a random number table (17). The first subject in each pair was administered caffeine on his first experiment and placebo on his second experiment, while the second subject in each pair was administered placebo on his first experiment and caffeine on his second experiment. All subjects, but not the investigators, were blinded as to which test beverage was being administered. Before testing, all subjects underwent a caffeine fast for 12 h and a complete fast for 6 h (except for ad lib oral water consumption) and had a full night’s sleep (5 h or more). All subjects were tested individually, each subject undergoing two separate experiments, on separate days. Although the literature supports a 12-h washout period for caffeine as being adequate (1), for safety reasons at least 24 h between experiments was maintained to minimize the potential for the development of acute decompression sickness.

Statistical analysis: Analysis was accomplished using statistical tests (replication of 2 × 2 Latin squares) applicable to two-period crossover experimental designs (18), to determine whether oral caffeine consumption had a significant effect on the tissue O₂ levels in human subjects exposed to a HBO₂ environment. The null hypothesis was that caffeine has no effect on tissue O₂ levels in a HBO₂ environment; the outcome measure was “increase in PtcO₂” during hyperbaric exposure. The analysis was applied to the changes in PtcO₂ in the right foot and chest of subjects from initial measurement (before drink administration at 1 atm abs breathing air) to final measurement (1 h after drink administration breathing 100% O₂ at 2.36 atm abs for 30 min). In addition, a standard t test was applied to the mean of the differences between baseline PtcO₂ measurements in the caffeine and placebo groups to analyze for possible variations.

Study risks: The risks to the subjects in this study are from two possible causes: 1) risks from caffeine; and 2) risks from hyperbaric exposure. Risks from hyperbaric exposure can be further subdivided into risks from increased pressure per se (barotrauma) and risks from HBO₂ (oxygen toxicity). Finally, there may be a synergistic effect of the combined risks of pressure, O₂, and caffeine.

Fatal poisoning by the ingestion of caffeine is rare. Although the short-term lethal dose of caffeine in adults seems to be about 5–10 g, untoward reactions may be observed following the ingestion of 1 g (15 mg · kg⁻¹; plasma concentrations above 30 μg · ml⁻¹) (16). Insomnia, restlessness, and excitement are early symptoms, which may progress to delirium; in addition, the muscles become tense and tremulous, tachycardia and extra systoles are frequent, and respiration is quickened; emesis and convulsions are also possible (16). Untoward effects of caffeine that would be most likely to occur with the doses used in this study protocol are nervousness, tremors, palpitations, dizziness, and increased respiratory rate (16).

Possible hazards associated with hyperbaric exposure to 2.36 atm abs include pulmonary O₂ toxicity (respiratory failure), central nervous system oxygen toxicity (seizures), decompression sickness, arterial gas embolism, and barotrauma (middle ear, craniofacial sinuses, mediastinum, intestines, pneumothorax) (19).

RESULTS

Analysis of the treatment effect between increases in the chest PtcO₂ values of subjects in the caffeine group and subjects in the placebo group demonstrates no significance, 104.6, 95% CI [-257.8, 48.6], P = 0.155. Analysis of the treatment effect between increases in the right foot PtcO₂ values in the caffeine group and in the placebo group demonstrates very strong significance, 268.4, 95% CI [133, 404], P = 0.0018. Thus, the increase in right foot PtcO₂ values is significantly smaller in the caffeine group than in the placebo group, whereas the chest PtcO₂ values show no significant change upon exposure to HBO₂.

Analysis of the differences between right foot baseline PtcO₂ values in the caffeine group and in the placebo group demonstrates no significance, 2.8, 95% CI [-58.8, 53.2], P = 0.91. Analysis of the differences between chest baseline PtcO₂ values in the caffeine group and in the placebo group demonstrates no significance, 8.2, 95% CI [-44.6, 61.0], P = 0.73. Figure 1 and Table 2 summarize the experimental data collected in this study.

DISCUSSION

This study shows that orally consumed caffeine, as compared with an orally consumed placebo, diminishes the

![FIG. 1—Experimental PtcO₂ during hyperbaric exposure.](image-url)
Table 2: Mean Absolute \( \text{PtcO}_2 \) Increases

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Caffeine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest mean absolute ( \text{PtcO}_2 ) increases, mmHg</td>
<td>1,150.8</td>
<td>1,255.4</td>
</tr>
<tr>
<td>Standard deviation, mmHg</td>
<td>219.9</td>
<td>141.0</td>
</tr>
<tr>
<td>Right foot mean absolute ( \text{PtcO}_2 ) increases, mmHg</td>
<td>836.4</td>
<td>568.0</td>
</tr>
<tr>
<td>Standard deviation, mmHg</td>
<td>261.5</td>
<td>210.7</td>
</tr>
<tr>
<td>Sample size, ( n )</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

increase of tissue \( O_2 \) levels in the right feet of healthy adult men induced by a HBO\(_2\) environment. Statistical analysis demonstrates that this effect is significant (\( P = 0.0018 \)) for the sample tested, within the experimental constraints of this study protocol. The diminished increase in \( O_2 \) levels noted in the feet were thought to be due to the peripheral vasoconstrictive effect of caffeine. The experimental findings support the practice of limiting caffeine use in patients undergoing HBO\(_2\) therapy.

The experimental results did not demonstrate a significant effect (at alpha = 0.1) of caffeine on arterial \( O_2 \) estimated from the chest electrodes (\( P = 0.155 \)). As described previously, the chest electrode provides an estimate of the central arterial \( O_2 \) partial pressure (12).

The argument could be made that in patients with problem wounds, many of whom have concurrent peripheral vascular disease, peripheral blood flow might already be so compromised that caffeine would not have any additional ischemic effect as measured by \( \text{PtcO}_2 \) values. Furthermore, there is the question of whether caffeine would have any effect on HBO\(_2\) therapy treatment outcome in these patients even if there were a decrease in their \( O_2 \) levels. Perhaps further experimentation in which caffeine would be administrated to actual patients with peripheral vascular disease and problem wounds, who are concurrently undergoing HBO\(_2\) therapy, would clarify these issues.

Although the experimental design of this study was chosen to minimize, within practical limits, potential biases and confounding factors, some inherent bias did remain. The \( O_2 \) electrodes themselves introduce a degree of inherent experimental error. These electrodes function by localized heating of the skin with a built-in electrical heating element to facilitate \( O_2 \) transfer across the dermal barrier as a result of cutaneous vasodilation and increased dermal permeability to oxygen. This localized vasodilatory effect apparently did not significantly alter the more widespread vasoconstrictive effect of caffeine, however, judging from the results obtained. Transcutaneous oxygen electrodes also manifest some degree of inherent variability in their readings, both from subject to subject and within the same subject (12). In addition, the electrode readings can be affected by such things as environmental temperature and pressure, patient movement and positioning, and electrode site placement (12). Despite the inherent variability and errors of transcutaneous tissue oxygen monitoring, it has been shown by previous studies (15), and by the results obtained in this study, that this method of measurement can be useful.

Based on the literature (1), the 12-h caffeine fast provides an adequate washout period for cardiovascular effects of caffeine in both chronic caffeine users and non-users. There are no known interactive effects of HBO\(_2\) on the pharmacokinetics of caffeine per se (20). Significant differences are found in the effects of caffeine between males and females (21), so conclusions based on these experimental results only apply to males.

Relatively large confidence intervals surrounding the experimental results were noted in this study. This is most likely a result of the relatively small number of subjects tested, primarily limited because of practical considerations associated with subject selection and availability. However, the crossover experimental design, being quite powerful, does allow for relatively small sample sizes, and significance was obtained in this experiment. Whether these differences would be clinically significant remains to be clarified by further studies involving clinical outcomes in actual hyperbaric patients.

In conclusion, based on the experimental evidence obtained in this study, we have observed that the consumption of caffeine in nominal doses significantly diminishes the increase of peripheral tissue \( O_2 \) levels of healthy male subjects exposed to a HBO\(_2\) environment. We believe that further scientific investigation would be warranted before extrapolating these findings to the general HBO\(_2\) patient population. Until such additional experimental clarification can be obtained, it is recommended that caffeine be restricted in HBO\(_2\) patients.

REFERENCES

CAFFEINE CONSUMPTION AND TISSUE OXYGEN LEVELS


