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Effects of hyperbaric exposure on eyes with intraocular gas bubbles

Stephen V. Jackman

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Yale University

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Effects of Hyperbaric Exposure on Eyes with Intraocular Gas Bubbles

A Thesis Submitted to the Yale University School of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

by

Stephen V. Jackman

1994

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Stephen V. Jackman

Signature of Author

January 18, 1994

Date

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PRESENTATIONS

This research has been previously presented at the following:

Association for Research in Vision and Ophthalmology (ARVO), Annual Meeting, May 1992, Sarasota, FL (Poster)

Student Research Day, May 1992, Yale University School of Medicine, New Haven, CT. (Poster)

Undersea and Hyperbaric Medical Society (UHMS), Annual Scientific Meeting, June 1992, Bethesda, MD (Platform talk)

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ABSTRACT

EFFECTS OF HYPERBARIC EXPOSURE ON EYES WITH INTRAOCULAR GAS BUBBLES. Stephen V. Jackman and John T. Thompson. Department of Ophthalmology and Visual Science, Yale University School of Medicine, New Haven, CT.

Air travel is known to be potentially hazardous for patients with intraocular gas bubbles (IGBs). These bubbles, which are used in the treatment of complicated retinal detachments, can last for up to a month depending on the combination of long-acting gases used. We hypothesized that the external pressure changes associated with hyperbaric oxygen therapy, SCUBA diving, or caisson work could be similarly dangerous.

To test this, we placed IGBs into the right eyes of 18 rabbits and exposed them to several hyperbaric pressure profiles. In all profiles, the intraocular pressure (IOP) in the left or control eyes remained constant while the IOP in the eyes with the IGB dropped to zero on pressurization and increased to over 50 millimeters of mercury (mmHg) on depressurization. Pressures in excess of 50 mmHg were sustained for 10 minutes or longer. The mean peak IOP of the eyes with the IGBs as well as the mean time spent at an IOP of over 50 mmHg were both highly significant compared to that of the control groups ($p < 0.001$).

This IGB-induced IOP response is caused by several mechanisms including

continued vitreous and aqueous fluid inflow with decreased outflow during hypotony, bubble volume increase due to equilibration with higher partial pressures of oxygen and nitrogen, and choroidal engorgement with delayed draining at high IOPs. The magnitude and duration over 50 mmHg of the IOPs measured were enough to potentially cause severe pain, occlusion of the central retinal artery, and retinal ischemia. We therefore strongly advise against hyperbaric exposure for patients with IGBs.

INTRODUCTION

1. Hypothesis and Statement of Purpose.

Intraocular gas bubbles (IGBs) are frequently used in vitreoretinal surgery to treat complicated retinal detachments.[1] They are absorbed gradually from the eye but may persist for days to months depending on the mixture of air and long acting intraocular gases used.[2] For example, a one milliliter bubble of 100% perfluoropropane (C_3F_8) injected into the vitreous chamber will diminish to half volume in 35 days and disappear in 70 days.[3]

Hyperbaric pressure is any pressure above the normal atmospheric pressure of one atmosphere absolute (ATA). Exposure to hyperbaric pressure occurs during hyperbaric oxygen therapy (HBOT), SCUBA diving, and caisson work. HBOT is standard treatment for diseases associated with intravascular gas bubbles, including decompression sickness and arterial gas embolism. It can be lifesaving in these instances. Additionally, HBOT is a valuable adjunctive treatment in conditions where increased oxygen needs to be delivered to specific tissues for acute preservation of viability or improved healing. HBOT continues to slowly gain popularity as more facilities and

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[1]Ai E, Gardner TW. Current patterns of intraocular gas use in North America. *Arch Ophthalmol* 1993; 111: 331-332.

[2]Lincoff H, Maisel J, Lincoff A. Intravitreal disappearance rates of four perfluorocarbon gases. *Arch Ophthalmol* 1984; 102: 928-929.

[3]Lincoff H, Coleman J, Kreissig I, et al. The perfluorocarbon gases in the treatment of retinal detachment. *Ophthalmology* 1983; 90: 546-551.

information regarding its appropriate use become available.

There are several studies and anecdotal reports that air travel and travel into the mountains from a lower altitude are potentially hazardous for those with IGBs.[4,5,6,7,8,9,10] This is due to the decrease in external atmospheric pressure which causes expansion of the gas bubble. With rapid decompression this expansion occurs faster than can be compensated for by increased aqueous outflow, mechanical choroidal compression, and scleral expansion. The result can be large increases in intraocular pressure (IOP) leading to severe pain and potential central retinal artery occlusion. The above studies led to the characterization of the size gas bubble which would be expected to cause a small and acceptable increase in intraocular pressure.

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[4]Aronowitz JD, Brubaker RF. Effect of intraocular gas on intraocular pressure. *Arch Ophthalmol* 1976; 94: 1191-1196.

[5]Brinkley JR Jr. Flying after vitreous injection. *Am J Ophthalmol* 1980; 90: 580-581.

[6]Fuller D. Flying and intraocular gas bubbles. *Am J Ophthalmol* 1981; 91: 276-277.

[7]Dieckert JP, O'Connor PS, Schacklett DE, et al. Air travel and intraocular gas. *Ophthalmology* 1986; 93: 642-645.

[8]Hanscom TA, Diddie KR. Mountain travel and intraocular gas bubbles. *Am J Ophthalmol* 1987; 104: 546.

[9]Lincoff H, Weinberger D, Reppucci V, Lincoff A. Air travel with intraocular gas. I. The mechanisms for compensation. *Arch Ophthalmol* 1989; 107: 902-906.

[10]Lincoff H, Weinberger D, Stergiu P. Air travel with intraocular gas. II. Clinical considerations. *Arch Ophthalmol* 1989; 107: 907-910.

They also developed recommendations for treatment in the event that a patient in flight was experiencing symptoms from increased IOP.[11]

Our hypothesis was that a hazard may exist in eyes with IGBs exposed to hyperbaric pressure. This hypothesis was based on the fact that similar changes in external pressure occur in both air travel and HBOT. Air travel consists of decompression on ascent and subsequent recompression back to normal atmospheric pressure on descent. HBOT, SCUBA diving, and caisson work consist of compression during descent and decompression on ascent. The hazard we specifically hypothesized was an increase in IOP during the decompression phase of hyperbaric exposure similar to that seen during the decompression phase of air travel. If there were a dangerous increase in IOP and if safe limits and treatment options were known, this information would be vital to the physician faced with a patient with an IGB and either the need for HBOT or the desire to go SCUBA diving or return to caisson work. Prior to this study, there had been no investigation into the interaction between hyperbaric exposure and intraocular gas. We therefore proceeded with the present study in an attempt to answer the following questions: Could hyperbaric exposure result in dangerous increases in IOP for patients with IGBs? If yes, are there conditions when it results in an acceptable and safe rise in IOP?

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[11]Lincoff H, Weinberger D, Stergiu P. Air travel with intraocular gas. II. Clinical considerations. *Arch Ophthalmol* 1989; 107: 907-910.

2. Intraocular Gas Bubbles in the Treatment of Retinal Detachment

Retinal detachment is the separation of the retina from the retinal pigment epithelium with the collection of fluid in the subretinal space. There are two recognized types of retinal detachment. The more common type is a rhegmatogenous detachment, meaning that a rip or tear is present in the retina. The less common serous or nonrhegmatogenous retinal detachment is caused by leakage of fluid from the choroidal or retinal vessels into the subretinal space and is usually caused by inflammatory diseases. Rhegmatogenous detachments demand immediate treatment to preserve retinal viability and visual acuity. Treatment centers on reattaching the retina to the underlying retinal pigment epithelium, its source of oxygen and nutrients.

Rhegmatogenous retinal detachments are the type of retinal detachment whose treatment can involve the use of IGBs. They develop when a break or tear in the retina allows vitreous cavity fluid to flow into the subretinal space and displace the retina. The tears are caused by vitreous traction which occurs as a result of partial vitreous liquefaction followed by partial posterior vitreous detachment with retention of some normal vitreoretinal attachments. Sudden acceleration or deceleration of the globe, either as a result of normal eye movements or trauma, can then pull on the retina and

cause a tear.[12] The cause of this series of events can be a spontaneous posterior vitreous detachment, prior ocular surgery, trauma, inflammatory or infectious processes, retinopathy of prematurity, and possibly topical miotic therapy.[13]

The IGB is placed in the vitreous cavity as part of the retinal detachment repair which may be done with a scleral buckle, vitrectomy, or pneumatic retinopexy. The function of the IGB is to close the retinal break and flatten the retina against the eyewall. This allows time for chorioretinal adhesions to form at the treatment sites and permanently reattach the retina. It takes at least eight days for retinal adhesion to be maximal.[14]

A bubble of normal air in the vitreous chamber has a half-life of only 1 to 1.5 days. It would be absorbed too quickly to dependably permit reattachment in many eyes. This has led to the choice of some more slowly absorbed inert gases for use as IGBs. Perfluoropropane (C_3F_8) and sulfur hexafluoride (SF_6) are the most commonly used. These gases have longer half-lives than air due to higher molecular weights, smaller diffusion

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[12]Vaughan DG, Asbury T, Tabbara KF. *General Ophthalmology, 12th ed.* East Norwalk, CT: Appleton and Lange, 1989; 176.

[13]Michels RG, Wilkinson CP, Rice TA. *Retinal Detachment.* St. Louis: Mosby, 1990; 234-5.

[14]Lincoff H, Coleman J, Kreissig I, et al. The perfluorocarbon gases in the treatment of retinal detachment. *Ophthalmology* 1983; 90: 546-551.

coefficients, and lower water solubility.[15] IGBs of 100% perfluoropropane or sulfur hexafluoride are only used when a very small volume is injected into the eye because they are expansile. They expand in size as the gas in the bubble equilibrates with the partial pressures of the gases in the vitreous fluid which in turn reflect the partial pressures in the inhaled air. Nonexpansile mixtures of gases which are approximately preequilibrated with the atmospheric air composition are used to prevent further expansion after IGB placement when large gas bubble volume is used.

The mechanisms of IGB action are the bubble's tamponade effect and direct hydraulic pressure. The tamponade effect functionally closes the retinal tear by occluding the retinal break, forming a barrier between the tear and any remaining vitreous cavity fluid. This prevents any new fluid from entering the subretinal space and allows the retinal pigment epithelial cells to absorb any fluid which might remain, thus allowing the retina to reattach to the eyewall. The bubble does not pass through the retinal break due to its surface tension which causes it to assume a spherical shape.[16]

The mechanical or hydraulic force of an IGB acts perpendicularly outward in all directions from the surface of the bubble. This forces the retina toward the eyewall and counteracts the hypotony which would result from

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[15]Michels RG, Wilkinson CP, Rice TA. *Retinal Detachment.* St. Louis: Mosby, 1990; 418.

[16]Michels RG, Wilkinson CP, Rice TA. *Retinal Detachment.* St. Louis: Mosby, 1990; 413.

uncompensated vitreous gel loss. The flotation force adds to the mechanical force in the vertical direction, further flattening the retina superior to the bubble and forcing the vitreous fluid to remain inferior to the break.[17] This aspect makes IGBs particularly useful in the treatment of superior retinal tears.

In summary, IGBs are established as an important part of retinal detachment treatment. Their long half-lives mean that many patients have IGBs for up to a month or more after surgery. During this time they would be otherwise well and able to undergo HBOT, SCUBA dive, or return to caisson work. This led us to examine the safety of hyperbaric exposure for patients with IGBs.

3. Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy is a treatment modality in which a patient breathes 100% oxygen intermittently at hyperbaric pressure.[18] As previously mentioned, HBOT can be either a lifesaving primary therapy or an adjunctive form of treatment. Recent statistics from the National Hyperbaric Registry indicate that 104,620 patients were treated with HBOT at 219 hyperbaric facilities in the United States and Canada from 1982 through

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[17]Michels RG, Wilkinson CP, Rice TA. *Retinal Detachment.* St. Louis: Mosby, 1990; 477.

[18]*Hyperbaric Oxygen Therapy: A Committee Report.* Bethesda, MD: Undersea and Hyperbaric Medical Society, 1989; 2-56.

1992.[19] This number will continue to climb in the future as less expensive monoplace chambers become available at more medical centers and as information regarding the benefits of HBOT becomes more widely disseminated. A recent review article in *JAMA* highlighted the increasing interest in HBOT and described the currently accepted indications[20].

There are two major mechanisms of action for HBOT. The first is pressure which reduces the volume of gas bubbles in the body as required by Boyle's Law ($P \propto 1/V$). At double atmospheric pressure (2 ATA), the pressure experienced at 10 meters or 33 feet under water, a bubble would be reduced to half its original volume. This mechanism is important in the treatment of decompression sickness (DCS) and arterial gas embolism (AGE) where intravascular gas bubbles are life-threatening. The reduction in bubble size prevents them from blocking arterioles and thus prevents large ischemic insults, most importantly in the cerebral vasculature.

The elevated pressure also increases the amount of gas able to be dissolved in the blood. This increases the rate at which the gas in the bubble goes into solution, especially if the patient is breathing pure oxygen. This dissolution further decreases the size of the bubbles and hinders the formation of new bubbles. Patients with DCS and AGE are often

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[19]National Hyperbaric Registry. Maryland Institute for Emergency Medical Services Systems (MIEMSS), January 1994.

[20]Grim PS, Gottlieb LJ, Boddie A, Batson E. Hyperbaric oxygen therapy. *JAMA* 1990; 263: 2216-2220.

compressed to 6 ATA (the equivalent of 50 meters or 165 feet under water) because of the highly beneficial effects of pressure in treating these diseases.

The second mechanism of HBOT action is an increased blood oxygen carrying capacity. Arterial partial pressures of oxygen ($p\bar{a}O_2s$) can reach 1800 millimeters of mercury (mmHg).[21] This huge increase over the normal $p\bar{a}O_2$ of 100 mmHg significantly elevates tissue partial pressures of oxygen (pO_2s). The benefits of such high oxygen tension are the acute support of tissue that might otherwise be irreversibly damaged. Secondary effects include vasoconstriction, increased immune function, and neovascularization in some tissues.

High oxygen tension induced vasoconstriction reduces swelling and vasogenic edema, notably cerebral edema. Although blood delivery is reduced, oxygen delivery is increased due to greatly increased $p\bar{a}O_2$ and decreased edema. The net result is better oxygenation and less edema.

Maintaining adequate oxygen delivery is critical in the functioning of certain cells of the immune system. Neutrophils require a pO_2 of at least 30 mmHg to generate their antimicrobial oxidative burst.[22] Neutrophil

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[21]Kindwall EP, Goldmann RW. *Hyperbaric Medicine Procedures, 6th revision.* Milwaukee, WI: St. Luke's Medical Center, 1988; 9.

[22]Hohn DC, MacKay RD, Halliday B, Hunt TK. The effect of O_2 tension on the microbicidal function of leukocytes in wounds and in vitro. *Surg Forum* 1976; 27: 18-20.

activation by HBOT in certain poorly vascularized areas can speed recovery from infections or abscesses.

High oxygen tension also promotes neovascularization of some tissues such as skin in areas of ischemic injury. Neovascularization requires oxygen dependent collagen synthesis by fibroblasts followed by capillary budding. The increased delivery of oxygen in a course of HBOT both facilitates collagen production at a considerably greater distance from existing capillaries than normally possible and forms a steeper than normal oxygen gradient between the established vessels and the hypoxic wound. These factors promote rapid capillary advancement.[23] HBOT is particularly efficient in this because it entails intermittent exposure to hyperbaric oxygen which is best for promoting capillary proliferation. Hypoxic periods are needed for macrophage mitogen-induced fibroblast replication and angiogenesis factor-induced capillary budding. Rapid neovascularization by HBOT is useful in the treatment of microvascularly compromised skin grafts.

Complications from HBOT are almost exclusively related to air-filled cavity barotrauma. Except for concurrent treatment with the chemotherapeutic agent cisplatin or doxorubicin, the only absolute contraindication for HBOT is

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[23]Knighton DR, Silver IA, Hunt TK. Regulation of wound-healing angiogenesis. Effect of oxygen gradients and inspired oxygen concentration. *Surgery* 1981; 90: 262-270.

untreated pneumothorax.[24] Some conditions in which caution must be exercised include upper respiratory infections, chronic sinusitis, history of spontaneous pneumothorax, history of thoracic surgery, history of reconstructive ear surgery, and pulmonary lesions. These all have the potential to sequester air in the body. This trapped air expands on decompression from hyperbaric exposure causing severe pain and damage to the surrounding tissue. The normal eye does not contain any gas and is not affected by high external pressure. However, the danger of barotrauma exists in eyes with intraocular gas bubbles. This could occur if the amount of gas in the bubble or the size of the vitreous chamber were altered as a consequence of hyperbaric exposure.

Other potential complications of HBOT include seizures induced by oxygen neurotoxicity and pulmonary toxicity. The only adverse ocular effect observed is an increased risk of cataract development in patients receiving more than 150 HBOT treatments. All of these are very rare with the treatment schedules used today.

The indications for HBOT include decompression sickness (DCS), gas embolism, carbon monoxide poisoning, Clostridial myonecrosis (gas gangrene), necrotizing faciitis and acute traumatic crush injury.[25,26] DCS,

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[24]Kindwall EP, Goldmann RW. *Hyperbaric Medicine Procedures, 6th revision.* Milwaukee, WI: St. Luke's Medical Center, 1988; 1.

[25]*Hyperbaric Oxygen Therapy: A Committee Report.* Bethesda, MD: Undersea and Hyperbaric Medical Society, 1989; 2-56.

more commonly known as "the bends", is the classic indication for HBOT. It is caused by a hyperbaric exposure of sufficient time and depth to give rise to inert gas nucleation on decompression. It occurs in divers, caisson workers, and less frequently by altitude exposure. The gas dissolved in the blood under pressure forms bubbles when the pressure is released too quickly for equilibration to take place. The symptoms of DCS include cutaneous eruptions (skin bends), joint pains (limb bends), neurological dysfunction (central nervous system bends), gas embolism, shock, and death. Recompression must be initiated as soon as possible for best resolution of symptoms. The failure to treat DCS can result in permanent peripheral nervous system, spinal cord, or brain damage as well as death.

Air or gas embolism, and especially arterial gas embolism, is a second clear indication for HBOT. Some causes include surgical procedures, predominately cardiac and neurosurgical cases, improper catheter use, intra-aortic balloon pump rupture, endoscopy, laser use, respirator malfunction, and chest or head trauma. Through its pressure effects, HBOT decreases bubble size and increases the gradient of diffusion out of the bubble as previously discussed.

HBOT's efficacy in other areas has been well documented.[27] In carbon

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[26]Grim PS, Gottlieb LJ, Boddie A, Batson E. Hyperbaric oxygen therapy. *JAMA* 1990; 263: 2216-2220.

[27]*Hyperbaric Oxygen Therapy: A Committee Report.* Bethesda, MD: Undersea and Hyperbaric Medical Society, 1989; 2-56.

monoxide poisoning, HBOT increases the rate of carbon monoxide elimination from hemoglobin and provides tissue oxygenation.[28] It significantly improves neurological and cardiac depression if given early, resulting in decreased morbidity in survivors. In Clostridial myonecrosis (gas gangrene) or other necrotizing soft tissue infections, HBOT added to a regimen of surgery and antibiotics can substantially decrease the tissue loss and need for amputations.[29,30] In crush injury and compartment syndrome, the high oxygen tension effects of vasoconstriction with decreased edema and increased oxygen delivery allow more frequent limb salvage and avoidance of surgical decompression.

In summary, HBOT has a wide variety of applications, some of which are emergently necessary for patient survival or restoration of normal mental function and others that are important for the sparing of limbs or soft tissue. A patient with an IGB certainly will have, or already has had, indications for HBOT. In light of this fact, it is necessary to examine the effects that HBOT would have on such a patient in order that an informed treatment decision can be made.

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[28]Pace N, Strajman E, Walker EL. Acceleration of carbon monoxide elimination in man by high pressure oxygen. *Science* 1950; 111: 652-654.

[29]Bakker DJ. Clostridial myonecrosis. In: Davis JC, Hunt TK eds. *Problem wounds. The role of oxygen.* New York: Elsevier Science Publishing, 1988; 170.

[30]Mader JT. Mixed anaerobic and aerobic soft tissue infections. In: Davis JC, Hunt TK eds. *Problem wounds. The role of oxygen.* New York: Elsevier Science Publishing, 1988; 181.

4. Proposal of a Test

To test our hypothesis on the interaction between hyperbaric exposure and intraocular gas bubbles, we chose to use rabbits as the experimental system. In this pilot experiment, we decided to use a medium-sized IGB of perfluoropropane (C_3F_8) and start with a mild hyperbaric exposure with respect to pressure and time. We planned to then increase the pressure and duration of the exposure up to the profiles of the standard U.S. Navy Treatment Tables and other hyperbaric treatment protocols. We hoped to define safe and unsafe limits of hyperbaric exposure with medium-sized IGBs and investigate to the best of our ability the causes of any effects observed during the exposure.

MATERIALS AND METHODS

1. Intraocular Gas Bubble Placement.

Eighteen medium-sized (2-3 kg) New Zealand White rabbits were used as the experimental system. The animals were treated in accordance with the guidelines established by the Association for Research in Vision and Ophthalmology and the protocol was approved by the Yale Animal Care and Use Committee. All the work in this study was done by myself with instruction and supervision by Dr. John T. Thompson who placed the IGBs in the first two rabbits.

The rabbits were systemically anesthetized with 25 mg/kg ketamine (Ketaset® - Aveco) and 5 mg/kg xylazine (Rompun® - Haver) injected intramuscularly into the haunch. When they were completely anesthetized, the right eye was exposed with a speculum and one drop of the local anesthetic proparacaine hydrochloride (Alcaine® - Alcon) was applied to the cornea. Using calipers, a point on the sclera was marked 2 millimeters posterior to the corneoscleral boundary just temporal to the blood vessels of the superior rectus muscle. The sclera was shallowly punctured at this point with a 30 gauge needle and 0.3 milliliters of 100% perfluoropropane (Matheson) was injected very slowly into the vitreous chamber. On removal of the needle, a cotton-tipped applicator was gently pressed against the site of injection to minimize the gas leakage as the eye returned to normal

pressure. A drop of gentamicin sulfate (Gentacidin® - IOLAB) was applied to prevent infection and the rabbits were returned to their boxes to recover.

The left eye was not injected and served as a control. The hyperbaric exposure took place approximately 48 hours after IGB placement. This allowed the bubbles time to equilibrate with the partial pressures of the gases dissolved in the fluid of the vitreous chamber. The equilibration process caused the bubbles to expand to fill about 60% of the vitreous cavity in each case.

2. Hyperbaric Exposure

The "dives" were performed at the Naval Submarine Medical Research Laboratory at the Naval Submarine Base in Groton, CT. After anesthesia administration, discussed below, they were transferred to a specially built cage for the dive. This cage had a plexiglass top and sides which prevented wind in the chamber from overcooling the rabbits and from spreading rabbit hair throughout the chamber.

The dives took place in a medium-sized walk-in hyperbaric chamber constructed by Bethlehem Steel (figures 1 and 2). The chamber was pressurized with compressed air and was vented several times during the dives to maintain a comfortable atmosphere. Carbon dioxide was continuously removed from the air by a scrubber in the chamber. The rabbits were accompanied on the dives by me. The dives were well

Figure 1. Hyperbaric Chamber. Outside View.

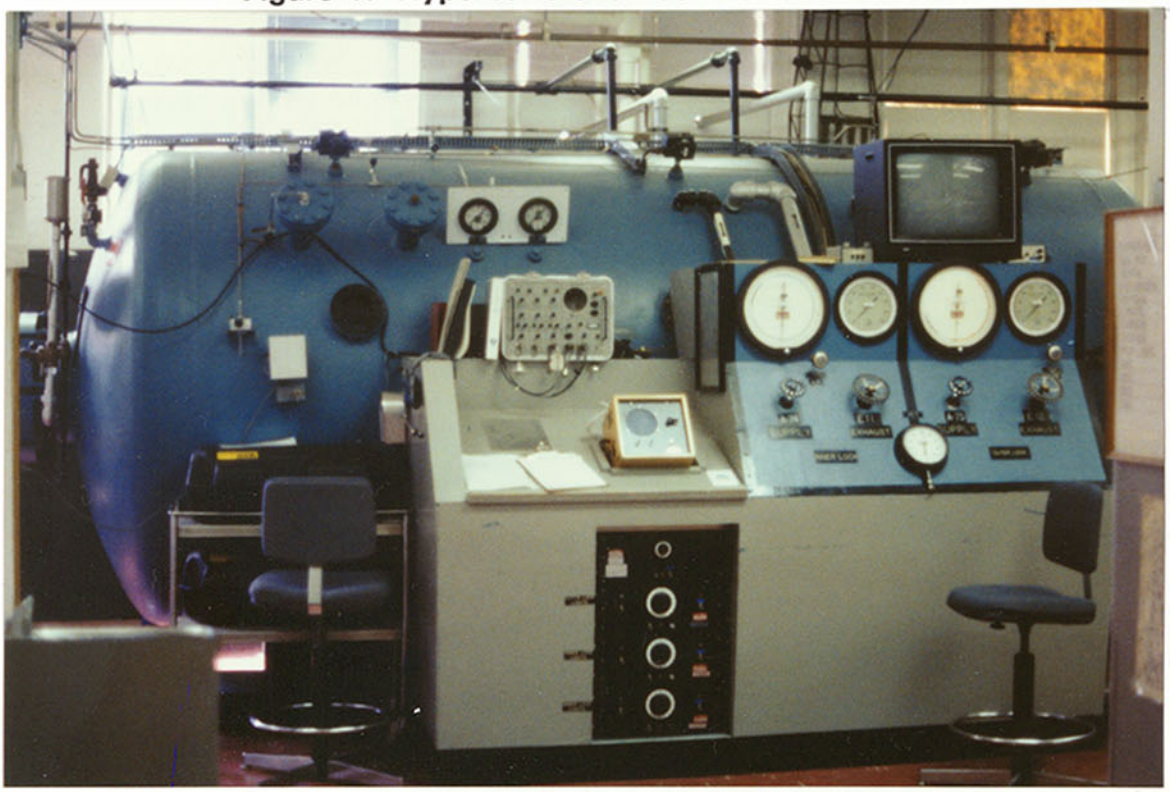
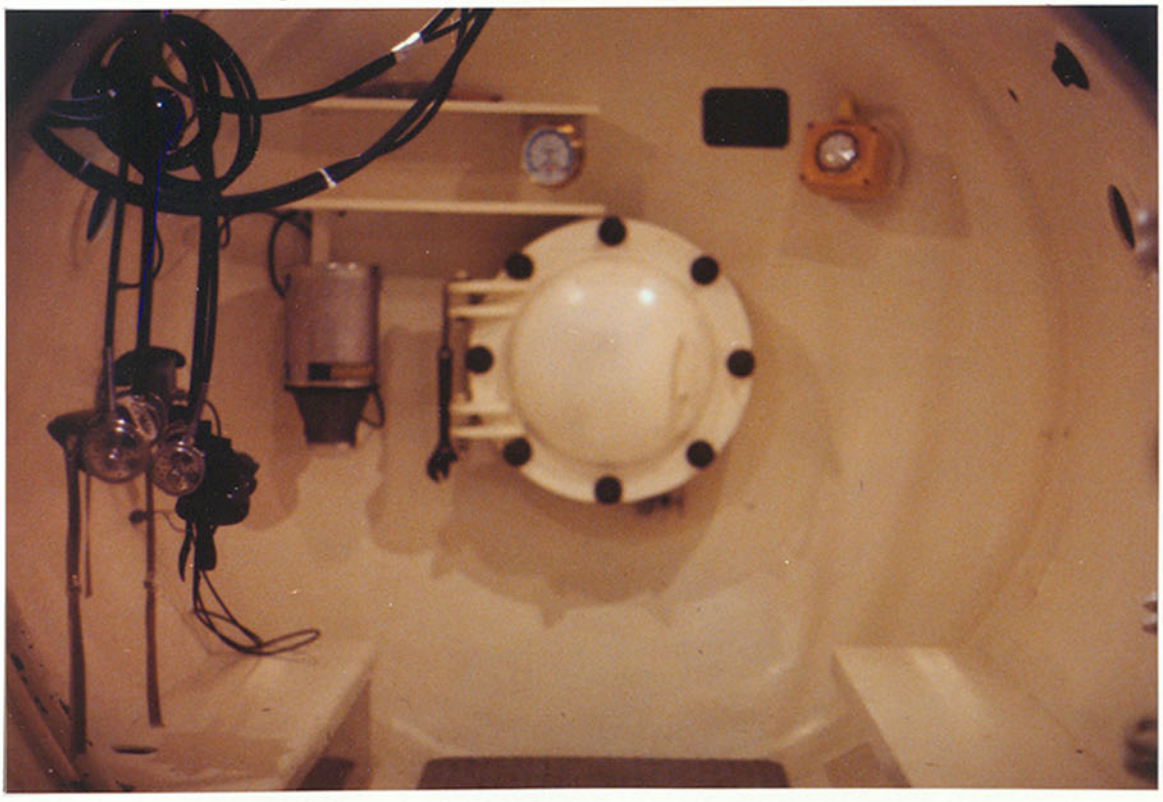


Figure 2. Hyperbaric Chamber. Inside View.



within the safety limits of the U.S. Navy Diving Manual and posed no danger of decompression sickness to either the investigator or the rabbits.[31] All dives were made to a pressure of 2.0 ATAs. This is equivalent to the pressure at a depth of 33 feet or 10 meters of sea water. The descent rate for all dives was 3.3 feet per minute giving a total descent time of ten minutes.

The rabbits were divided into four groups and each group was subjected to a different dive or hyperbaric exposure profile. The number of rabbits in each group and the dive profile including bottom time and ascent rate for each group is indicated in table 1. Group 1 rabbits were not dived. Group 2 rabbits spent 30 minutes at 2 ATAs ("Bottom Time") and then ascended or decompressed at 1 ft/min ("Ascent Rate"). Group 3 was identical to Group 2 except they spent only 1 minute at 2 ATAs. Group 4 also spent 1 minute at 2 ATAs but ascended at a rate of 0.2 ft/min, five times slower than Groups 2 and 3. The profiles can be compared graphically with each other and the U.S. Navy Treatment Table 5[32] in figure 3. The dive profile is also indicated on the graph of the typical IOP response data for each group.

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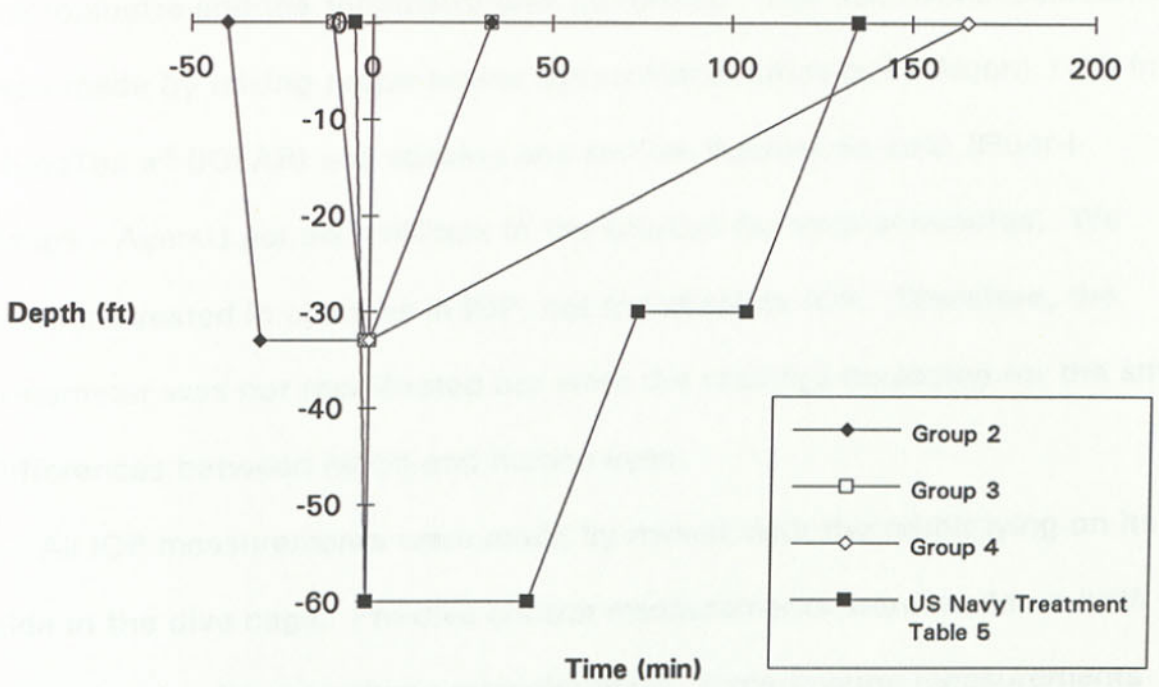
[31] *US Navy Diving Manual. Volume 1: Air Diving. Revision 2.* NAVSEA 0994-LP-001-9010. Washington, DC: US Government Printing Office, 1988; 7-31.

[32] *US Navy Diving Manual. Volume 1: Air Diving. Revision 2.* NAVSEA 0994-LP-001-9010. Washington, DC: US Government Printing Office, 1988; 8-52.

Table 1. Dive profiles by group and rabbit number

Group	Rabbit Number	Bottom Time (min)	Ascent Rate (ft/min)	Ascent Time (min)
1	1 - 4	no dive	no dive	no dive
2	5 - 12	30	1.0	33
3	13 - 16	1	1.0	33
4	17 - 18	1	0.2	165

Figure 3. Hyperbaric exposure profiles compared.



Zero time is defined as the start of ascent.

3. Intraocular Pressure Measurement.

Intraocular pressure was measured on anesthetized rabbits by applanation tonometry. The rabbits were systemically anesthetized with Telazol® (AH Robins), a combination drug consisting of tiletamine and zolazepam. This drug was chosen because it does not appreciably affect intraocular pressure. The dose used depended on the length of the dive. Typically a 30 mg/kg induction dose was given, followed by 15 mg/kg doses about every 50 minutes as needed.

The IOP was measured with a Kowa applanation tonometer. A drop of fluorescein and topical anesthetic solution was given from a capillary micropipette and the tonometry was performed. The fluorescein solution was made by mixing proparacaine hydrochloride (Alcaine® - Alcon) 1:10 in HypoTears® (IOLAB) and soaking one sodium fluorescein strip (Fluor-I-Strip® - Ayerst) per six milliliters in the solution for several minutes. We were interested in changes in IOP, not the absolute IOP. Therefore, the tonometer was not recalibrated nor were the readings corrected for the small differences between rabbit and human eyes.

All IOP measurements were made by myself with the rabbit lying on its side in the dive cage. Pre-dive control measurements were made on both eyes shortly after anesthetic administration. Experimental measurements were made at intervals throughout and after the dive. Smaller intervals were used as needed when the IOP was changing rapidly. Measurement was

stopped when the experimental eye IOP returned to normal or when the rabbit was too awake to make further measurements. The Kowa tonometer was only capable of determining IOPs of up to 60 mmHg. Thus, values of greater than 60 mmHg had to be recorded as 60 mmHg for statistical purposes.

4. Other Procedures.

Post-dive paracentesis and aqueous protein concentration estimation was done on two rabbits in Group 3. After the dive but while the animals were still under anesthesia, one drop of proparacaine hydrochloride (Alcaine® - Alcon) was applied to the cornea. The cornea was then punctured obliquely using a tuberculin syringe with a 27 gauge needle. Approximately 0.1 ml of aqueous was collected. This was done to both the left and right eyes of the two rabbits. The samples were diluted and transferred to quartz cuvettes. The optical density at 280 nanometers was determined by ultraviolet spectrophotometry.[33]

Bubble size estimation was done grossly on the same two rabbits by measuring the bubble meniscus height in the vitreous cavity using the

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[33]Cantor CR, Schimmel PR. *Biophysical Chemistry. Part II: Techniques for the study of biological structure and function. Absorption spectroscopy.* New York: WH Freeman and Co., 1980; 380-381.

technique developed by Dr. Thompson.[34] The rabbit was placed with its head in the upright position and the investigator observed the rabbit's eye from the same horizontal level. The size of the bubble was recorded as the location of the meniscus in relationship to the pupil.

The rabbits were housed and monitored for any complications at the Yale animal care facilities before and after both the bubble insertion and the dives.

5. Data analysis.

The data were tabulated on an IBM®-compatible computer running Excel® 3.0 (Microsoft). All tables and graphs were generated by this program. The amount of time spent at an IOP of over 50 mmHg was estimated to the nearest minute by hand from the IOP graph for each rabbit. The data were analyzed for significance using a two-tailed Student t-test. The p values were read off a standard chart.[35]

6. Exceptions.

There were two exceptions to the above protocol. During ascent in the

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[34]Wong RF, Thompson JT. Prediction of the kinetics of disappearance of sulfur hexafluoride and perfluoropropane intraocular gas bubbles. *Ophthalmology* 1988; 95: 609-613.

[35]Zar JH. *Biostatistical Analysis.* Englewood Cliffs, NJ: Prentice-Hall, 1974; 413.

first dive a stop was made during ascent at 8 feet for 21 minutes due to concern over the high pressure in one of the experimental eyes. This prolonged the time at high IOP for these two Group 2 rabbits (#5 and #6). They were therefore not used in figuring the mean time with IOP over 50 mmHg for Group 2. The second exception is that much of the gas from the right eyes of three Group 2 rabbits (#7, #9, and #10) leaked out immediately following injection of perfluoropropane. The data from these eyes were thus excluded from the analysis. The left eye of one of these rabbits (#7) was successfully filled with gas and used as the experimental eye for that rabbit. The other two left eyes were used normally as controls.

RESULTS

1. Raw Data.

The raw intraocular pressure data for each rabbit are presented by group and dive in the appendix. The data from one rabbit in each group are graphically displayed in figures 4 through 7 to show a typical IOP response for that group. The dive depth profile is included on the bottom half of these figures for correlation of the IOP response with the current depth and stage of the dive.

Figure 4. Group 1: No Dive
Typical IOP Response

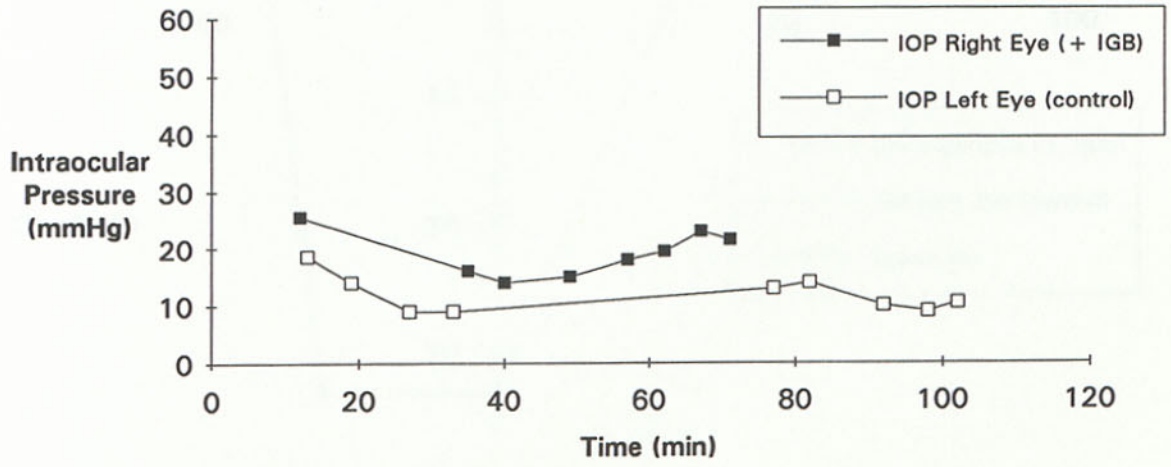


Figure 5. Group 2: Original Dive Profile
Typical IOP Response

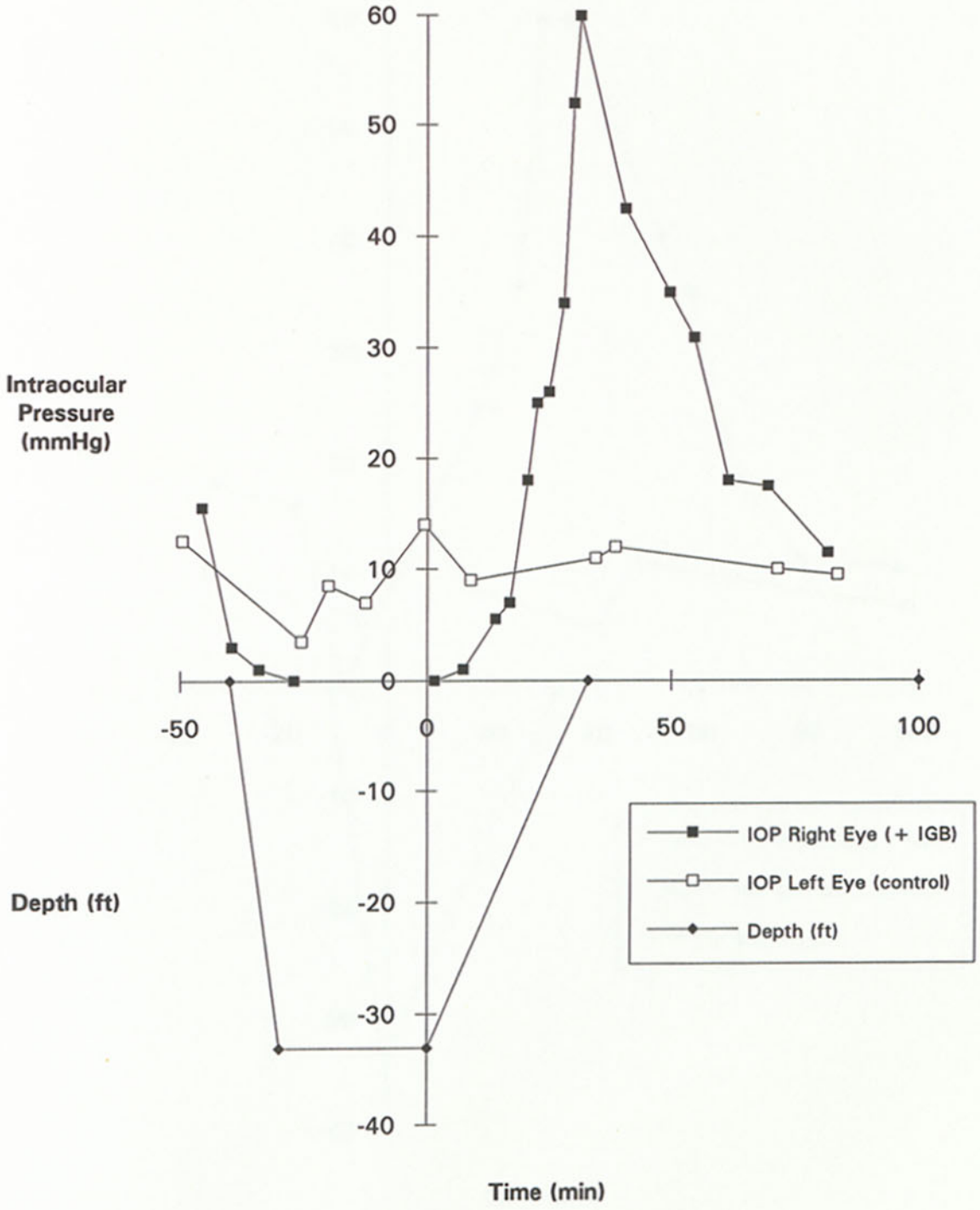


Figure 6. Group 3: Short Bottom Time
Typical IOP Response

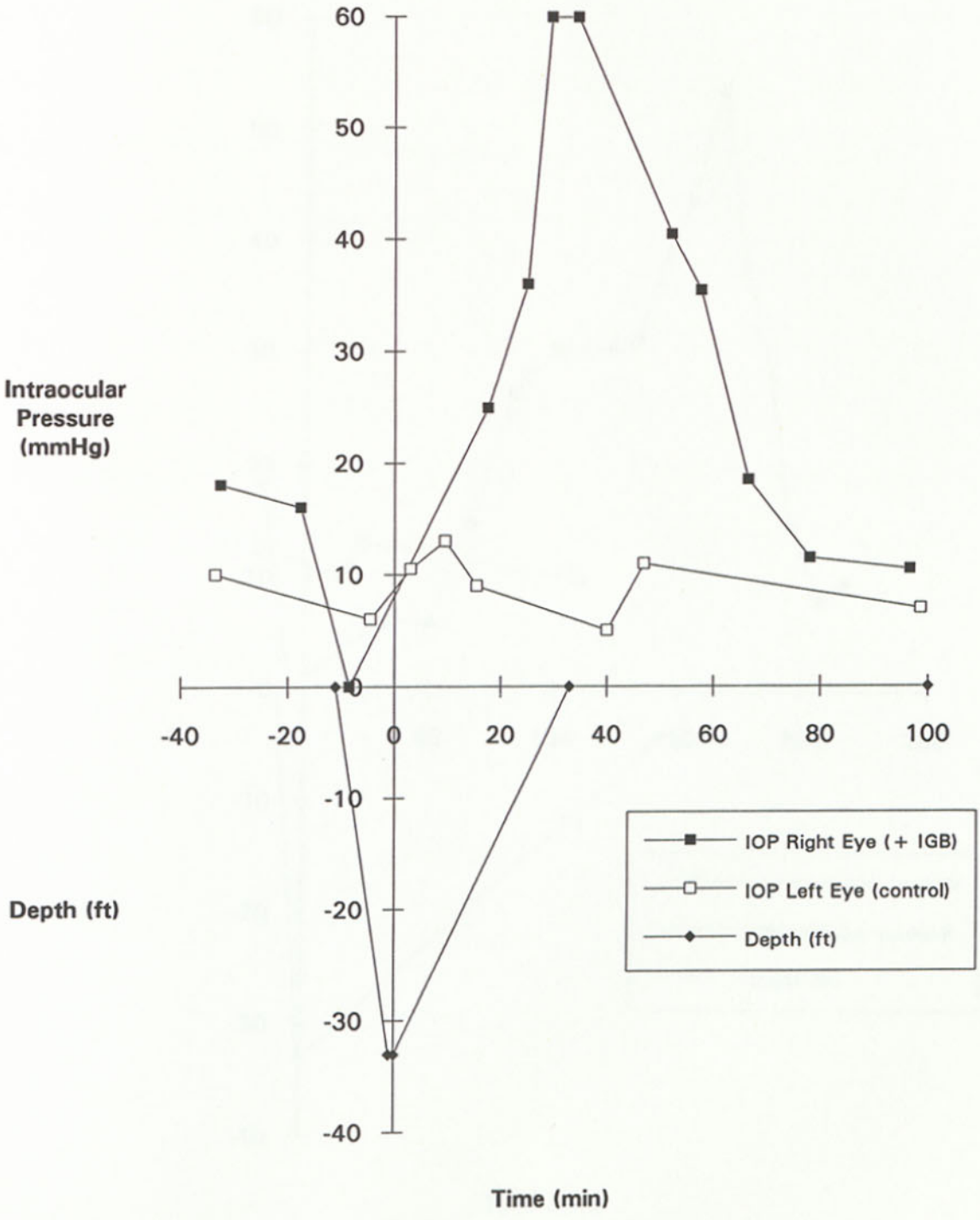
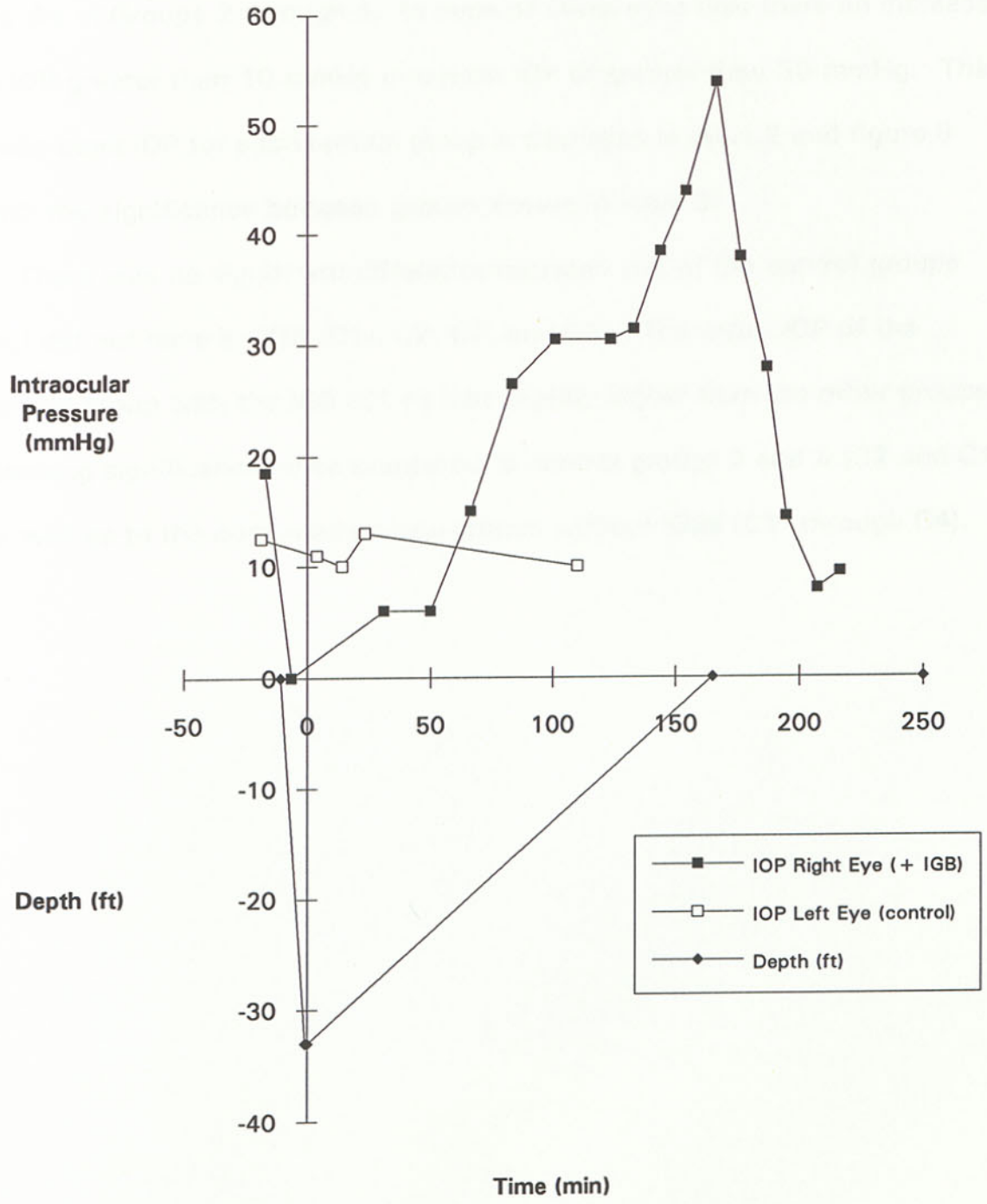


Figure 7. Group 4: Short BT & Slow Ascent
Typical IOP Response



2. Control Data.

The control groups consisted of eyes that were not dived, did not have an IGB, or both. This includes all the eyes in Group 1 and the left eyes of the rabbits in Groups 2 through 4. In none of these eyes was there an increase in IOP greater than 10 mmHg or a peak IOP of greater than 30 mmHg. The mean peak IOP for each control group is displayed in table 2 and figure 8 with the significance between groups shown in table 3.

There was no significant difference between any of the control groups that did not have an IGB (C1-, C2, C3, and C4). The mean IOP of the control group with the IGB (C1+) was slightly higher than the other groups, reaching significance when compared to control groups 2 and 4 (C2 and C4) as well as to the combined control groups without IGBs (C1- through C4).

Table 2. Mean Peak IOPs for Control Groups

Group	IGB	N	Dive Profile	Mean Peak IOP (mmHg)
C1 +	Y	4	Group 1	21
C1-	N	4	Group 1	19
C2	N	7	Group 2	15
C3	N	4	Group 3	15
C4	N	2	Group 4	14
C1- to C4	N	17	Groups 1-4	16

Fig. 8. Mean Peak IOPs for Control Groups

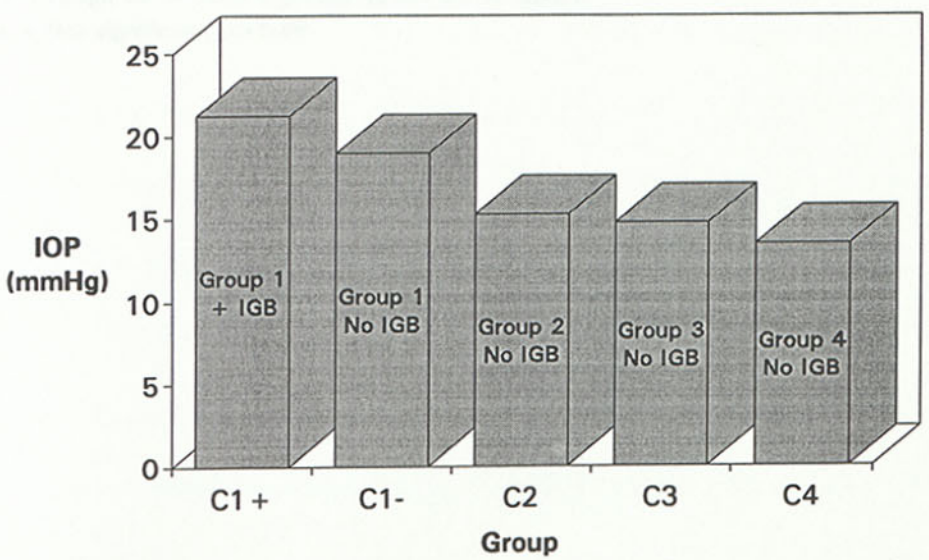


Table 3. Significance Between Peak IOPs of Controls

Groups Compared	t value	Degrees of Freedom	p value
C1+* & C1-*	0.59	6	ns**
C1+ & C2*	3.34	9	<0.02
C1+ & C3*	1.94	6	ns
C1+ & C4*	2.91	4	<0.05
C1- & C2	1.35	9	ns
C1- & C3	0.96	6	ns
C1- & C4	1.08	4	ns
C2 & C3	0.22	9	ns
C2 & C4	0.98	7	ns
C3 & C4	0.29	4	ns
C1+ & C1- to C4	2.22	19	<0.05

*C1+ through C4 = Control groups as defined in Table 2

**ns = Not significant, p>0.05

3. Experimental Data.

The experimental groups consisted of eyes with IGBs that were dived. This includes the right eyes of Groups 2 through 4. The IOP of all of these eyes increased by greater than 30 mmHg and peaked above 50 mmHg. This is best seen in the typical IOP response figures: 5, 6, and 7 (pages 25-27). Despite the different depth profiles, the three experimental groups showed very similar IOP responses consistently related to specific stages of the dive. Seconds after beginning the dive, the IOP of all the right eyes dropped to zero. It remained zero for the entire bottom time. Shortly after beginning the ascent the IOP began to rise. The maximal rate of rise occurred in the last 10 feet of ascent and the IOP peaked at the surface. This was followed by a slow decline back to baseline IOP over a period of 40 to 50 minutes.

The peak IOP and the amount of time spent at an IOP of over 50 mmHg was determined for each eye. The mean peak IOP and the mean time over 50 mmHg were then calculated for each group. The results are displayed in table 4 and figures 9 and 10. Figure 9 clearly demonstrates that the mean peak IOP was 21 and 16 mmHg for the control groups but over 50 mmHg for each of the experimental groups. This difference was very highly significant for each group compared to the each of the controls ($p<0.005$). The difference between Groups 2 and 4 also reached significance with $p<0.05$ (table 5).

Similarly, figure 10 shows that none of the controls developed an IOP

greater than 50 mmHg while all the experimental groups spent 10 or more minutes over 50 mmHg IOP. Again, the difference between the control groups and each of the experimental groups was very highly significant ($p<0.001$). Although the mean time for Group 4 was only 10 minutes as compared to 17 for the other two groups, this difference was not significant possibly due to the small number of data points (table 6).

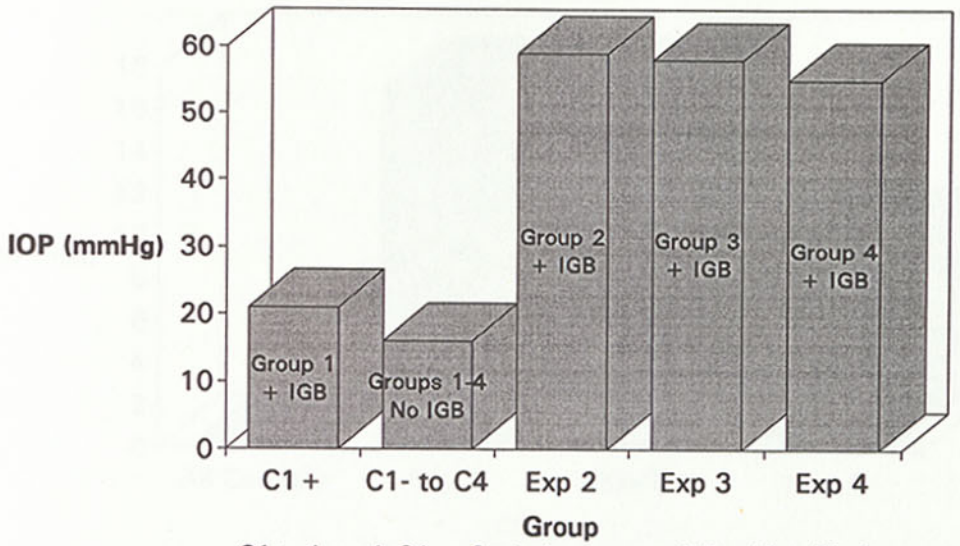
Table 4. IOP response data

Group	N	Mean Peak IOP (mmHg)	Mean Time Over 50 mmHg (min)
C1+*	4	21	0
C1- to C4*	17	16	0
Exp 2**	6/4	59	17
Exp 3**	4	58	17
Exp 4**	2	55	10

*C1+ through C4 = Control groups as defined in Table 2

**Exp 2,3, & 4 = Experimental eyes of the respective group

Figure 9. Mean Peak IOPs



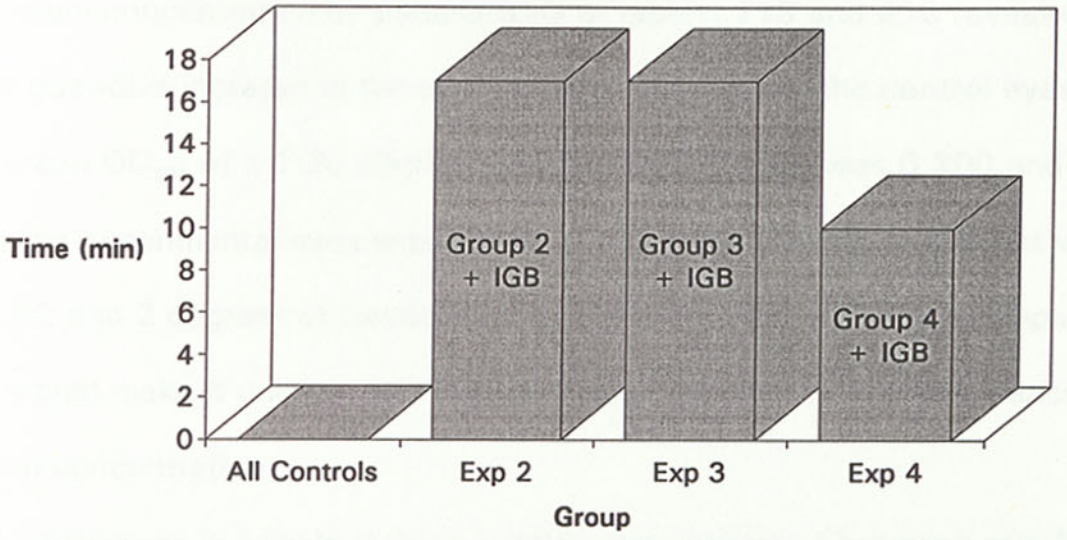
C1 + through C4 = Control groups as defined in table 2
Exp 2, 3, & 4 = Experimental eyes of the respective group

Table 5. Significance between Peak IOP values

Groups Compared	t value	Degrees of freedom	p value
C1 +* & Exp 2**	3.99	10	<0.005
C1 + & Exp 3**	13.79	6	<0.001
C1 + & Exp 4**	12.44	4	<0.001
C1- to C4* & Exp 2	22.47	23	<0.001
C1- to C4 & Exp 3	16.79	19	<0.001
C1- to C4 & Exp 4	11.88	17	<0.001
Exp 2 & Exp 3	0.62	8	ns***
Exp 2 & Exp 4	2.62	6	<0.05
Exp 3 & Exp 4	0.98	4	ns

*C1 + through C4 = Control groups as defined in table 2
**Exp 2,3, & 4 = experimental eyes of the respective group
***ns = not significant (p>0.05)

Figure 10. Mean Time Over 50 mmHg



Exp 2, 3, & 4 = Experimental eyes of the respective group

Table 6. Significance between Times Over 50 mmHg

Groups Compared	t value	Degrees of freedom	p value
Controls & Exp 2*	6.09	23	<0.001
Controls & Exp 3*	7.76	23	<0.001
Controls & Exp 4*	170.77	21	<0.001
Exp 2 & Exp 3	0.06	6	ns**
Exp 2 & Exp 4	0.68	4	ns
Exp 3 & Exp 4	0.83	4	ns

*Exp 2,3, & 4 = experimental eyes of the respective group

**ns = not significant (p>0.05)

4. Other Data.

Protein concentration by paracentesis of rabbits #15 and #16 revealed a small post-dive increase in the experimental eyes versus the control eyes. The mean OD_{280} of a 1:20 dilution from the control eyes was 0.300 and from the experimental eyes was 0.430. This result was not significant with $t = 1.32$ and 2 degrees of freedom giving $p > 0.20$. But, the small sample size would make it unlikely to detect anything less than a large difference in protein concentration.

No difference in bubble meniscus height was observed between pre-dive and post-dive observations of rabbits #15 and #16. The meniscus was at the lower border of the pupil, giving an approximate bubble size of 60% of the vitreous cavity in both cases.

DISCUSSION

1. Support of Hypothesis.

The results clearly show that exposure of an IGB-containing eye to our hyperbaric pressure profiles results in a dramatic rise in IOP. This increase occurs specifically when the external pressure decreases back to normal atmospheric pressure. The elevation in IOP is both of sufficient magnitude and duration to cause severe pain, decreased blood flow to the retina, and possible permanent visual loss. Transient central retinal artery occlusion can occur at IOPs of 45 mmHg and greater.[36]

2. Possible Mechanisms.

The reason for the observed increase in IOP is not obvious. According to Boyle's Law ($P \propto 1/V$), the volume of the bubble is expected to decrease by one half as the external pressure doubles. This accounts for the immediate fall in IOP at the beginning of the dive. As the pressure returns to normal, the bubble should return to its original size and bring the eye back to its starting IOP. This is contrary to our findings, indicating that other physiologic factors contribute to increasing the IOP. There are two explanations: either the volume of the bubble on return to normal pressure

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[36]Dieckert JP, O'Connor PS, Schacklett DE, et al. Air travel and intraocular gas. *Ophthalmology* 1986; 93: 642-645.

has increased, or the effective size of the vitreous chamber containing the gas bubble has decreased.

There are several possible mechanisms for bubble expansion or effective decrease in vitreous chamber size. The first is that the amount of fluid in the eye may increase during the time of the dive. Attempted reexpansion of the gas bubble to its original size would then cause an increase in IOP which would last until the fluid volume returned to its pre-dive quantity. Fluid volume in the eye could increase by both ciliary body secretion of normal aqueous and by an imbalance of the steady-state Starling forces allowing net fluid movement into the eye.

Ciliary body aqueous production is normally balanced by trabecular meshwork outflow. During the relative hypotony induced by bubble compression, the IOP is less than episcleral venous pressure causing trabecular meshwork collapse and significantly decreased outflow.[37]

The normal fluid balance of the eye is determined by a Starling-type equilibrium, with the hydrostatic and protein oncotic pressures of the eye balanced against those of the surrounding tissue. The sudden decrease in hydrostatic pressure within the IGB-containing eye as occurred during HBOT would shift the equilibrium and allow net fluid inflow. One paper suggests that the potential water movement across the choroid is enough to replace

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[37]Johnstone MA, Grant WM. Pressure-dependent changes in structures of the aqueous outflow system of human and monkey eyes. *Am J Ophthalmol* 1973; 75: 365-383.

half the vitreous volume in as short as 11 minutes, although their methods are currently in question.[38] Regardless, both these elements certainly contribute to some extent to increasing the intraocular fluid volume and thus the IOP as the bubble reexpands. This elevation would last until outflow mechanisms could restore the fluid balance. A further complicating factor is that high IOP is known to increase outflow resistance by partial occlusion of the trabecular meshwork.[39] This would have contributed to extending the duration of the high IOP.

A second mechanism is increase in size of the gas bubble during the time required for the dive. The eyes were injected with pure perfluoropropane 48 hours before the dive. Most of the bubble expansion is known to occur within 48 hours with the period of most rapid expansion being in the first six hours.[40,41] The one to three hour duration of the dive would not be expected to be associated with substantial further expansion under normal atmospheric conditions. This is confirmed by the observation that the control rabbits which were not dived showed only a slightly elevated IOP as

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[38]Kinsey VE, Grant M, Cogan DG. Water movement and the eye. *Arch Ophthalmol* 1942; 27: 242-252.

[39]Davson H. *Physiology of the Eye, 5th ed.* New York: Pergamon Press, 1990; 19.

[40]Crittenden JJ, de Juan E, Tiedeman J. Expansion of long-acting gas bubbles for intraocular use: Principles and practice. *Arch Ophthalmol* 1985; 103: 831-834.

[41]Hilton GF, Grizzard WS. Pneumatic retinopexy: A two-step operation without conjunctival incision. *Ophthalmology* 1986; 93: 626-641.

compared to the controls without IGBs, and no large increases in IOP during the control dive time period. However, there is evidence that altered partial pressures of gases in the blood during N_2O anesthesia can cause significant expansion of previously stable IGBs in short periods of time.[42] Exposure to hyperbaric air at 2 ATA doubles the partial pressures of oxygen and nitrogen in the blood. This causes the bubble to expand as oxygen and nitrogen enter the bubble, composed of perfluoropropane, oxygen, and nitrogen, to equilibrate with the new environment. On ascent, the bubble reequilibrates back toward 1 ATA but any lag in equilibration would result in a bubble larger than the original bubble and an increased IOP. Slowing the ascent would allow the bubble more time to reequilibrate and thus should minimize the IOP increase due to this mechanism. This is likely to be part of the explanation for the lower mean peak IOP and time over 50 mmHg IOP for Group 4. We could not measure the rate of reequilibration but did exclude a large post-dive change in bubble volume by measuring bubble size pre- and post-dive.

A third mechanism is increase in choroidal thickness induced by the period of hypotony. Possible causes for this include choroidal engorgement with blood or interstitial fluid, choroidal effusion and hemorrhagic choroidal

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[42]Wolf GL, Capuano C, Hartung J. Effect of nitrous oxide on gas bubble volume in the anterior chamber. *Arch Ophthalmol* 1985; 103: 418-419.

detachment.[43] These effectively decrease the total intravitreal volume. Expansion of the gas bubble in the now smaller chamber would lead to increased IOP. This would last until the choroid returned to normal. Drainage of blood from an engorged choroidal bed is hindered by the fact that increased IOP decreases the pressure gradient for flow from the choroidal veins to the vortex veins.[44] There were no choroidal or retinal detachments noted but we did not test this theory directly. We did observe that the episcleral and conjunctival vessels became engorged in the eye with the intraocular gas bubble after the dive although this could have been a secondary effect from the hypotony or elevated IOP.

Another mechanism considered was breakdown of the blood-aqueous barrier. This would have led to increased protein in the anterior chamber, possibly resulting in a plasmoid aqueous which passes poorly through the trabecular meshwork and can by itself cause large rises in IOP.[45] Bubble expansion would have further aggravated this situation. Blood-aqueous barrier breakdown was originally reported as a consequence of a sudden

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[43]Dieckert JP, O'Connor PS, Schacklett DE, et al. Air travel and intraocular gas. *Ophthalmology* 1986; 93: 642-645.

[44]Mäepea O. Pressures in the anterior ciliary arteries, choroidal veins and choriocapillaries. *Exp Eye Res* 1992; 54: 731-736.

[45]Davson H. *Physiology of the Eye, 5th ed.* New York: Pergamon Press, 1990; 54.

decrease in IOP.[46] Prostaglandin release has been shown in one study to be necessary for this to occur.[47] The small increase in aqueous protein concentration indicates a minimal breakdown of the blood-aqueous barrier. An increase in protein of over one hundred-fold would be expected if there were a massive breakdown and secretion of a plasmoid aqueous.[48]

3. Shortcomings.

The shortcomings of this study consist of three types: first, technical problems carrying out the study; second, limitations of the study that cause it to differ from actual exposure of a human with an IGB to hyperbaric pressure; and third, limitations in the amount of data able to be collected in a fixed period of time with finite resources. We had only two technical problem of note. The first was the early difficulty with gas leakage immediately after IGB injection. This was due to my personal inexperience with the procedure. With practice and slight modifications in technique, we had no further problem with gas leakage. The gas leakage did result in three eyes with substantially less than the 0.3 ml original bubble volume. These

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[46]Wessely K. Experimentalle Untersuchungen ü. d. Augendruck, sowie über qualitative und quantitative Beeinflussung des intraokularen Flussigkeitswechsels. *Arch Augenheilk* 1908; 60: 97-160.

[47]Al-Ghadyan A, Mead A, Sears M. Increased pressure after paracentesis of the rabbit eye is completely accounted for by prostaglandin synthesis and release plus pupillary block. *Invest Ophthalmol Vis Sci* 1979; 18: 361-365.

[48]Davson H. *Physiology of the Eye, 5th ed.* New York: Pergamon Press, 1990; 19.

were appropriate for use neither as control nor experimental eyes within the study design. They were therefore excluded from the data analysis. We chose to dive these rabbits in spite of the leakage and interestingly, some of these eyes with smaller IGBs showed perceptible but smaller increases in IOP. It would be useful in the future to study the IOP response using a series of smaller bubbles of known sizes.

The second technical problem involved the Kowa applanation tonometer used. As previously mentioned in the materials and methods section, it could only read a maximum IOP of 60 mmHg. The majority of the experimental eyes reached pressures exceeding 60 mmHg and thus, their true peak IOPs were underestimated. Fortunately, the difference between the experimental and control eyes was so clear that it did not alter the conclusions of the study. However, differences between the experimental groups were severely blunted, only just reaching a significance of $p<0.05$ between the mean peak IOPs of Groups 2 and 4. The Kowa tonometer was not ideal in other respects as well. It allowed only intermittent measurement of IOP. Too frequent measurement would increase the aqueous outflow secondary to the pressure of the tonometer on the cornea. Thus, the IOP could be artificially lowered. This possibility was minimized by spacing out the readings to no more than one per five minutes except when absolutely necessary. This resulted in less data points than desired, but certainly sufficient to answer our hypothesis.

The limitations of the study with regard to study design include the use of a rabbit model, the use of hyperbaric air and not oxygen, the method and timing of IGB insertion, and the use of Telazol® anesthesia. First, the rabbit eye is a good but not perfect model for study. Its scleral rigidity is lower than that of the human eye and the outflow facility is somewhat higher.[49,50] This would suggest that the IOP elevation may be even more pronounced in human eyes.

Second, we used hyperbaric air rather than oxygen. Had pure oxygen been used, the partial pressures of oxygen and nitrogen in the vitreous fluid would have been significantly altered. The lower partial pressure of nitrogen would have caused the diffusion of nitrogen out of the bubble rather than into the bubble as with the hyperbaric air. Oxygen, on the other hand, would have had a much steeper gradient to diffuse into the bubble. We did not have the equipment to use hyperbaric oxygen to test the net effect of this situation on IOP response. Our results are therefore most valid for exposure to hyperbaric air as occurs in SCUBA diving, caisson work, and the air-breathing intervals of HBOT. A second possible effect of using hyperbaric oxygen is oxygen-induced choroidal and retinal blood vessel

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[49]McEwen WK, St. Helen R. Rheology of the human sclera. Unifying formulation of ocular rigidity. *Ophthalmologica* 1965; 150: 321-346.

[50]Prince JH. Aqueous drainage. 3. Outflow. In: Prince JH, ed. *The Rabbit in Eye Research.* Springfield, IL: Charles C Thomas Publishers, 1964; 336-337.

constriction.[51,52] This would have the result of reducing any contribution to increased IOP from choroidal engorgement.

Third, we injected small bubbles of 100% perfluoropropane by very fine needle into the vitreous cavity. They then greatly expanded over the next 48 hours to give us the approximately 60% vitreous chamber size bubbles we desired. From the comparison between the IOP of the control groups with and without IGBs, it is apparent that control eyes with IGBs had slightly higher IOPs than those without. This may be due to the fact that the bubbles were still expanding slowly even after 48 hours. Or, it could be a result of the surgical manipulation. In the human, a nonexpansile mixture of air and long-acting gas is usually placed after vitrectomy and retinopexy. This type of bubble changes size only slightly as it equilibrates exactly to the vitreous milieu during the first 24 hours. Operative placement of the IGB, was not feasible in our study and it is difficult to hypothesize how the response of the post-operative eye would differ from that of the eyes in this study. It is possible that the increase in IOP could be greater or more damaging in eyes after recent surgery.

Fourth, people exposed to HBOT, SCUBA diving and caisson work are not generally anesthetized. We, however, needed to anesthetize the rabbits

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[51]Gallin-Cohen PF, Podos SM, Yablonski ME. Oxygen lowers intraocular pressure. *Invest Ophthalmol Vis Sci* 1980; 19: 43-48.

[52]Nichols CW, Lambertsen CJ. Effects of high oxygen pressures on the eye. *N Engl J Med* 1969; 281: 25-30.

throughout the dive. The systemic dissociative anesthetic Telazol® was chosen for its minimal effect on IOP. This is confirmed by the fact that none of our control eyes showed consistent increases or decreases in IOP after Telazol® injection. This limitation, we believe, had minimal effect on our data.

The final set of limitations to our study are related to finite resources and time. In this first study ever into the effects of hyperbaric exposure on eyes with IGBs, our primary objective was to determine whether it could be dangerous. To this end, we chose to use medium-sized bubbles and start with a mild hyperbaric pressure profile. If there were an effect, we then planned to characterize it and determine its causes to the extent of our time and resources. The most limited resource was hyperbaric chamber time. After considerable negotiating, the Navy was gracious enough to donate the use of their facilities and personnel for a maximum of seven sessions. Following the first couple dives, it was clear that the answer to our original question was yes, it is dangerous. This gave us enough time to alter one of the variables of the study and begin to characterize the limits of the IOP response. We also made additional measurements on some of the last rabbits to test some of our theories on the mechanisms causing the increase in IOP.

The variable we changed was dive profile. We chose to leave the bubble size constant and attempt to determine if there were any safe dive profile for

that bubble size. We first reduced the bottom time from 30 minutes to 1 minute in group 3 to give less time for vitreous and aqueous fluid inflow during the phase of hypotony. This did not appreciably decrease the marked elevation in IOP upon ascent to the surface. We then additionally slowed the ascent rate from 1 ft per minute to 0.2 ft per minute in group 4. This was done to see if increased time for aqueous outflow, bubble reequilibration, and choroidal draining would decrease the rise in IOP. The IOP still became dangerously elevated although the peak IOP was not as high, nor the time above 50 mmHg as long. If we had had the resources, we would have continued with our characterization of a safe dive profile and a safe bubble size. We could also have made more aqueous protein measurements and bubble size estimates. But, these must now be relegated to future studies.

4. Further Work Needed.

From analyzing the shortcomings of this study, it is clear that much further work is needed. Some of the areas where this is needed are: improved IOP measurement, the use of eyes which are more similar to human eyes, the effect of breathing pure oxygen, making the measurements in post-operative eyes, analyzing the mechanisms of IOP increase, and the effect of different IGB sizes and dive profiles.

Improved IOP measurement would ideally be capable of accurately

measuring all encountered IOP values, provide continuous IOP measurement, not affect the IOP, and be noninvasive. The best solution to this is probably cannulation of the anterior chamber. It is invasive, but it otherwise fulfills the criteria.

This study cannot be performed in humans, but the use of pig eyes or some other species with eyes similar to humans would be desirable. Ideally, these eyes should have a comparable scleral rigidity and aqueous outflow to humans. This data would give a better estimate of the effects of IGBs and HBOT in humans eyes.

The effect of breathing pure oxygen as opposed to air at hyperbaric pressures would be relatively easy to measure. The experiments need to either be performed in a small hyperbaric chamber pressurized with oxygen or a nonrebreather mask for the rabbit needs to be used. The former would be possible if anterior chamber cannulation were used to measure the IOP because the investigator would then not need to be in the chamber with the rabbit. The latter requires only that the proper equipment be obtained.

Similarly, only the proper equipment and personnel are required to test the response of a post-operative rabbit eye to the increased IOP. The animals could be dived at various times after the operation to simulate the combined effect of bubble size and recent intraocular surgery.

Elucidation of the proportional contributions of each of the hypothesized mechanisms for the increased IOP is important. The contribution of the

temporary increase in bubble size to increased IOP could be isolated from the possible effects of decreased aqueous outflow and choroidal engorgement by accurately measuring the volume of the gas bubble before, during, and after the HBOT. These measurement could also be done with enucleated eyes to minimize choroidal engorgement and water flow into the eye. The existence of choroidal thickening could be determined by observation with the correct instruments or by sacrifice of the animal when the IOP is high, followed by sectioning of the choroid and microscopy to determine if choroidal edema, effusion or hemorrhagic detachment are present.

Much future work needs to be done using different sized bubbles and different hyperbaric pressure profiles in order to define safe limits, if any, of the combination of hyperbaric exposure and IGBs. We have started this task by using three different dive profiles but only the mildest began to show a slight decrease in the IOP response. The ascent in that profile was already very slow. Substantially slower ascents are likely to be impractical. We did not examine the effects of smaller bubbles except by accident due to gas leakage. From this small amount of data there seems to be more promise in investigation in this direction.

CONCLUSION

Marked elevation in intraocular pressure occurs during hyperbaric exposure in patients with an intraocular gas bubble. This is probably caused by several mechanisms including continued vitreous and aqueous fluid inflow with decreased outflow during hypotony, bubble volume increase due to equilibration with higher partial pressures of oxygen and nitrogen, and choroidal engorgement with delayed draining at high IOPs. We cannot, at this stage, define with certainty the proportional contribution of each but further experimentation should clarify these issues. The use of rabbits, a mild HBOT profile and hyperbaric air are limitations of the current study. With the less stretchable sclera of the human eye and use of accepted HBOT treatment tables or SCUBA diving profiles, even larger increases in IOP would be expected.

Elevation in IOP during flying with an intraocular gas bubble is treated by having the plane descend a few thousand feet.[53] The treatment of elevated IOP during hyperbaric exposure is more problematic since a more rapid return to sea level would exacerbate the elevation in IOP. A very slow ascent could be considered but our study showed that increased IOP developed even during a very slow ascent of 0.2 feet/minute. The only definitive treatment would be aspiration of the intravitreal bubble with a

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[53]Lincoff H, Weinberger D, Stergiu P. Air travel with intraocular gas. II. Clinical considerations. *Arch Ophthalmol* 1989; 107: 907-910.

needle placed into the eye.

The data strongly suggest that hyperbaric exposure be avoided in patients with intraocular gas bubbles except in extreme circumstances. If HBOT must be performed emergently, removal of part of the intravitreal gas bubble may be needed to prevent dangerous elevation in IOP during ascent. Patients inquiring about SCUBA diving or return to caisson work should also be warned that these must be avoided until the intraocular gas bubble has been fully absorbed.

ABBREVIATIONS

AGE	Arterial Gas Embolism
ATA	Atmosphere Absolute, 1 ATA = normal atmospheric pressure
DCS	Decompression Sickness
HBOT	Hyperbaric Oxygen Therapy
IGB	Intraocular Gas Bubble
IOP	Intraocular Pressure
mmHg	Millimeters of Mercury, 760 mmHg = 760 torr = 1 ATA
$p\bar{a}O_2$	Arterial Oxygen Tension
pO_2	(Tissue) Oxygen Tension

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Ai E, Gardner TW. Current patterns of intraocular gas use in North America. *Arch Ophthalmol* 1993; 111: 331-332.

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APPENDIX

Table A1. Raw Data for Group 1 - No Dive

Control Dive #A RABBIT #1:

Comment	Time R	IOP R
No Dive	12	17
	20	13
	30	11
	34	8
	46	4
	52	4

Comment	Time L	IOP L
No Dive	8	20
	23	8
	28	11
	36	9
	42	11
	54	11
	60	9
	80	12

RABBIT #2:

Comment	Time R	IOP R
No Dive	14	22
	27	22
	31	17
	40	15
	48	13
	57	13.5
	79	12.5

Comment	Time L	IOP L
No Dive	18	27
	25	14
	33	13
	38	13
	50	12
	55	12

Table A1 cont. Group 1

Control Dive #B RABBIT #3:

Comment	Time R	IOP R
No Dive	12	25.5
	35	16
	40	14
	49	15
	57	18
	62	19.5
	67	23
	71	21.5

Comment	Time L	IOP L
No Dive	13	18.5
	19	14
	27	9
	33	9
	77	13
	82	14
	92	10
	98	9
	102	10.5

RABBIT #4:

Comment	Time R	IOP R
No Dive	10	20.5
	16	16
	22	14.5
	31	18.5
	42	14
	43	12.5
	48	14
	55	13
	60	13
	66	17.5
	69	16
	75	17.5
	80	16
	85	16
	90	19
	95	17
	100	17
	105	16
	110	18
	115	17
	120	16.5
	125	16

Comment	Time L	IOP L
No Dive	8	10.5
	37	5

Time R/L = Dive time = Number of minutes post-injection of anesthetic for the control dives

IOP R/L = Intraocular pressure in mmHg of the corresponding eye

Table A2. Raw Data. Group 2 - 30 Minutes Bottom Time

DIVE #1 RABBIT #5:

Comment	Time R	IOP R
Predive	-52	16
Descent	-36	0
	-34	0
	-22	0
	-15	0
	-9	0
	-1	0
Ascent	1	0
	4.5	0
	8.5	1
	11.5	3
	15	1
	18	2
	21.5	2
	29.5	6
	35	3
	46.5	13.5
	47	12
Surface	62	53
	70	60

Comment	Time L	IOP L
Predive	-55	14
Descent	-20	18
	-16	16
	-6	16
Ascent	23	5
	27.5	4
	37	10.5
Surface	60	9

RABBIT #6:

Comment	Time R	IOP R
Predive	-49	20
Descent	-32	0
	-24	1
	-18	1
	-7	2
	0	5
Ascent	3.5	8.5
	6	8.5
	10.5	18
	13	32
	17	41
	20.5	56
	24	60
	30	60
	40	60
Surface	64	60
	68	60

Comment	Time L	IOP L
Predive	-50	13
Descent	-30	17
	-25	13
	-3	9
Ascent	44	10

Table A2 cont. Raw data. Group 2

DIVE #2 RABBIT #7:

Comment	Time R	IOP R
Predive	-54	12
Descent	-32.5	2
	-22	2
	-15.5	1
	-9.5	0.5
	-3.5	2
Ascent	6.5	1.5
	10	4
Surface	32.5	41.5
	42	30.5
	53	18
	57	14
	80	9.5

Comment	Time L	IOP L
Predive	-52.5	8.5
Descent	-38.5	7.5
	-30	2
	-23.5	0
	-2	2
Ascent	5	4
	12	4
	15	7.5
	19	23
	21.5	27.5
	23.5	34.5
	27	41
	29	42
	31	60
Surface	43.5	47.5
	51.5	35.5
	60	24.5
	67.5	15
	78.5	9.5

RABBIT #8:

Comment	Time R	IOP R
Predive	-45.5	15.5
Descent	-39.5	3
	-34	1
	-27	0
Ascent	1.5	0
	7.5	1
	14	5.5
	17	7
	20.5	18
	22.5	25
	25	26
	28	34
	30	52
	31.5	60
Surface	40.5	42.5
	49.5	35
	54.5	31
	61.5	18
	69.5	17.5
	81.5	11.5

Comment	Time L	IOP L
Predive	-49.5	12.5
Descent	-25.5	3.5
	-20	8.5
	-12.5	7
	-0.5	14
Ascent	9	9
Surface	34.5	11
	38.5	12
	71.5	10
	83.5	9.5

Table A2 cont. Raw data. Group 2

DIVE #3 RABBIT #9:

Comment	Time R	IOP R
Predive	-50	6
Descent	-36.5	0
	-6.5	0
	-1	0
Ascent	1	0
	4.5	0
	8	0
	14.5	0.5
	18.5	1.5
	21.5	2
	25	3.5
	28	4
	32	12
Surface	35.5	17.5
	46	7.5
	56	4
	61	4
	71	5

Comment	Time L	IOP L
Predive	-51	11
Descent	-35	11
	-23	10
	-15.5	6
	-10	8
Ascent	9.5	11
	12.5	10
Surface	38	10
	74.5	13.5

RABBIT #10:

Comment	Time R	IOP R
Predive	-43	11
Descent	-32.5	0.5
	-5.5	2.5
	-0.5	3.5
Ascent	1.5	3
	5	3.5
	8.5	6.5
	15.5	12
	19	18.5
	22.5	24.5
	26	30.5
	29	33.5
	32.5	41
Surface	36	45
	47	29.5
	54	20
	62.5	14.5
	72	8.5

Comment	Time L	IOP L
Predive	-46.5	11
Descent	-30.5	18.5
	-21	8.5
	-13.5	8
	-8.5	8.5
Ascent	11	7
	13.5	5
Surface	39.5	8.5
	77	8

Table A2 cont. Raw data. Group 2

DIVE #4 RABBIT #11:

Comment	Time R	IOP R
Predive	-49	20
Descent	-38.5	2
	-33	0
Ascent	27.5	53
	30	60
Surface	38	60
	46	60
	52	60
	58	60
	66	47
	78	44
	88	30
	99	24.5
	105	13

Comment	Time L	IOP L
Predive	-50	8
Descent	-30	9
	-24	12
	-18.5	11
	-13	11
	-7.5	10
	-1	11
Ascent	3	12
	9	9
	14	13
	18.5	11
	22.5	8.5
	26	8.5

RABBIT #12:

Comment	Time R	IOP R
Predive	-45	16.5
Descent	-36.5	0
	-26	0
	-2.5	0
Ascent	1.5	0
	5.5	0
	10.5	0
	15.5	0
	20.5	4.5
	24	5
	28.5	27
	31	50
Surface	39	55
	44.5	45
	50.5	46
	59	48
	67	37
	79	42
	90	23
	100	14.5

Comment	Time L	IOP L
Predive	-46	13
Descent	-21.5	7

Time R/L = Dive time in minutes, 0 is defined as the start of ascent

IOP R/L = Intraocular pressure in mmHg of the corresponding eye

Table A3. Raw Data. Group 3 - 1 Minute Bottom Time

DIVE #5 RABBIT #13:

Comment	Time R	IOP R
Predive	-20.5	21
Descent	-8.5	0
Ascent	25.5	46.5
	29	60
Surface	33.5	60
	49	60
	57.5	51
	66.5	42
	74.5	36
	82.5	30
	90.5	27
	96.5	23.5
	103.5	16

Comment	Time L	IOP L
Predive	-22	11
Descent	-4.5	15
Ascent	2	15.5
	12.5	14.5
	23.5	15.5
Surface	36.5	16
	46.5	20

RABBIT #14:

Comment	Time R	IOP R
Predive	-16	19
Descent	-7	0
Ascent	4.5	1
	14.5	2.5
	22	5.5
	27	22.5
	30.5	37.5
Surface	35	52
	44	42
	56	31
	64.5	18.5
	73	13
	81.5	12

Comment	Time L	IOP L
Predive	-18.5	7.5
Surface	87.5	4

Table A3 cont. Raw data. Group 3

DIVE #6 RABBIT #15:

Comment	Time R	IOP R
Predive	-35.5	19
	-18.5	25
Descent	-9.5	1
	-7	1
	-2	3
Ascent	4.5	17
	7.5	24
	12.5	34
	19	37.5
	23.5	46
	28.5	60
Surface	33.5	60
	53.5	13
	58.5	10
	68.5	8

Comment	Time L	IOP L
Predive	-40.5	18.5
Surface	50.5	9.5
	80	8.5

RABBIT #16:

Comment	Time R	IOP R
Predive	-32.5	18
	-17.5	16
Descent	-8.5	0
Ascent	17.5	25
	25	36
	29.5	60
Surface	34.5	60
	52	40.5
	57.5	35.5
	66.5	18.5
	78	11.5
	96.5	10.5

Comment	Time L	IOP L
Predive	-33.5	10
Descent	-4.5	6
Ascent	3	10.5
	9.5	13
	15.5	9
Surface	40	5
	47	11
	98.5	7

Time R/L = Dive time in minutes, 0 is defined as the start of ascent

IOP R/L = Intraocular pressure in mmHg of the corresponding eye

Table A4. Raw Data. Group 4 - 1 Minute Bottom Time and Slow Acent

DIVE #7 RABBIT #17:

Comment	Time R	IOP R
Predive	-20	24
Descent	-8.5	0
Ascent	30	1
	48	2.5
	65	6.5
	82	22.5
	100	31.5
	122	30.5
	132	38.5
	142	38
	153	42
Surface	166	56
	175	31
	196.5	24.5
	206	15
	215.5	13.5

Comment	Time L	IOP L
Predive	-22	14
Descent	-1.5	13
Ascent	13	11.5
	22.5	12
	108.5	12

RABBIT #18:

Comment	Time R	IOP R
Predive	-17	18.5
Descent	-6.5	0
Ascent	31	6
	50	6
	66.5	15
	83.5	26.5
	101	30.5
	123.5	30.5
	133	31.5
	144	38.5
	154.5	44
Surface	167	54
	176.5	38
	187	28
	195	14.5
	207.5	8
	216.5	9.5

Comment	Time L	IOP L
Predive	-18.5	12.5
Ascent	4	11
	14	10
	23.5	13
	110	10

Time R/L = Dive time in minutes, 0 is defined as the start of ascent

IOP R/L = Intraocular pressure in mmHg of the corresponding eye