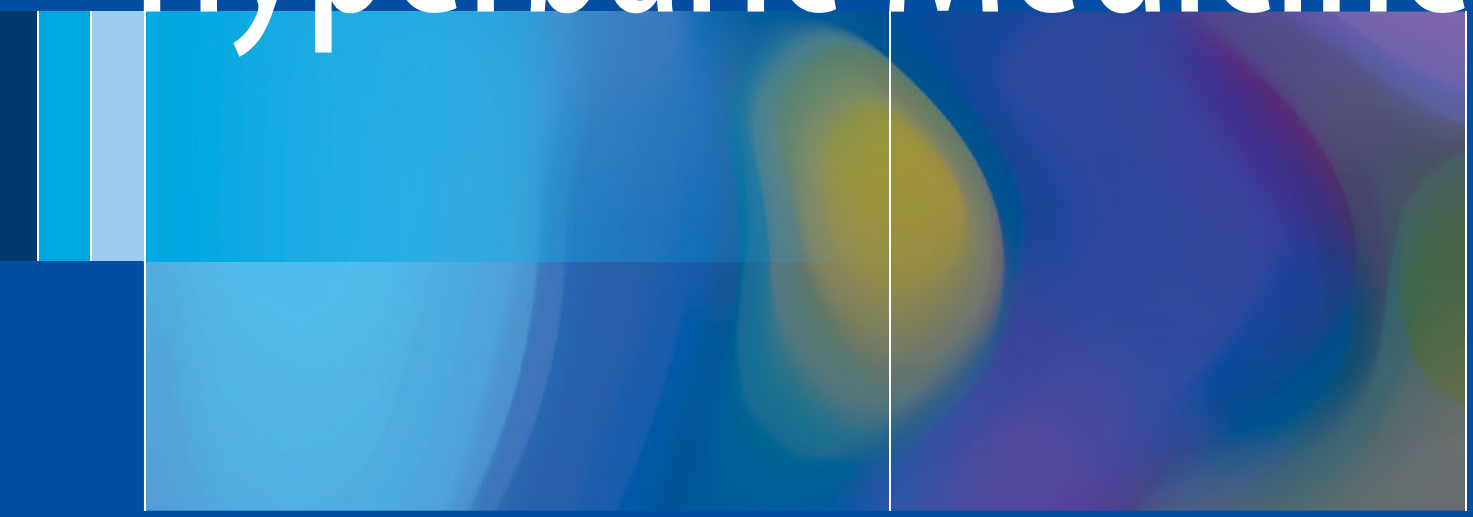
Kewal K. Jain

Textbook of Hyperbaric Medicine



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The History of Hyperbaric Medicine

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K.K. Jain

Abstract

This chapter reviews the historical relationship between hyperbaric therapy and diving medicine, recounting the important stages in the development of compressed-gas technology and a few of the more interesting early attempts to utilize it for medical purposes.

Keywords

Compressed air • Diving medicine • History • Hyperbaric chambers • Hyperbaric medicine • Oxygen

Hyperbaric Therapy and Diving Medicine

As is well known, the origins and development of hyperbaric medicine are closely tied to the history of diving medicine. While the attractions of the deep are easily understood, it was the various unpleasant physical consequences of venturing beneath the surface of the world's oceans that led directly to the many applications of compressed-gas therapy in modern medicine. Although scientifically based applications of hyperbaric technology are a relatively recent development, the use of compressed gas in medicine actually has ancient roots.

The origin of diving is not known, but it was recognized as a distinct occupation as far back as 4500 BC. However, since humans can only hold their breath for a few minutes, unaided dives are limited to depths of less than about 30 m. The first use of actual diving equipment to extend the limits of underwater activity is attributed in legend to none other than Alexander the Great, who, in 320 BC, is said to have been lowered into the Bosphorus Straits in a glass barrel (Fig. 1.1), which purportedly gave him a secret weapon in the siege of Tyre.

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Around the year 1500, Leonardo Da Vinci made sketches of a variety of diving appliances, without developing any for practical use. It was not until 1620 that the Dutch inventor Cornelius Drebbel developed the first true diving bell. His device was extremely limited, especially by its simple air supply that delivered air pressurized at only one atmosphere, but it was certainly the forerunner of all submersible vehicles.

In 1691 Edmund Halley, after whom the comet is named, advanced diving bell technology by devising a method of replenishing the air supply using weighted barrels (Smith 1986). This was followed in the next two centuries by the development of compressed-air diving helmets and suits, which made it possible to remain under water for an hour or more.

Even though the duration of dives had been extended, divers were still limited to the same shallow waters as before. Undersea pioneers had quickly discovered the eardrum-rupturing effects of increasing water pressure. Those attempting to venture even deeper in diving bells also quickly learned about the best-known medical problem associated with diving: decompression sickness. It was not until the middle of the nineteenth century that the effectiveness of countering decompression sickness with hyperbaric recompression was finally discovered (Table 1.1). Although recompression in air was utilized first, hyperbaric oxygen (HBO) is now used, and this is the principal connection between diving medicine and the other forms of HBO therapy.

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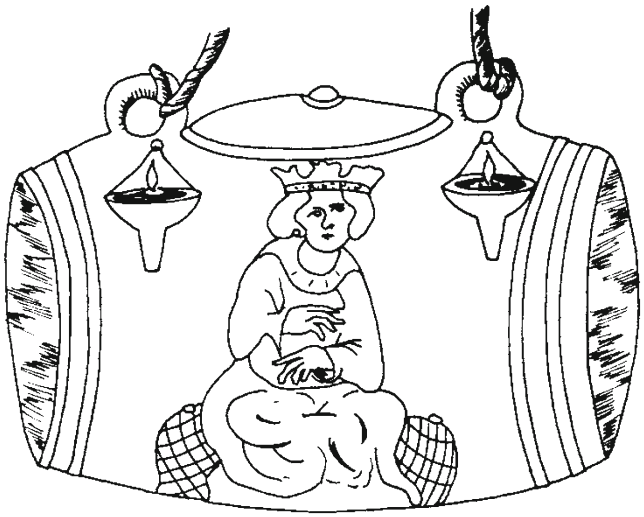

Fig. 1.1 Alexander the Great was said to have been lowered into the Bosphorus Straits in a glass barrel. Note that the candles are lighted and if, indeed, Alexander went into this barrel, he was lucky to survive. The illustration is redrawn from a thirteenth century manuscript in the Burgundy Library in Brussels and is reproduced courtesy of Dr. E. B. Smith

Table 1.1 Some important benchmarks in the history of diving medicine in relation to hyperbaric medicine

4500 BC	Earliest records of breath-holding dives for mother-of-pearl
400 BC	Xerxes used divers for work on ships and for salvaging sunken goods. Dives were for 2–4 min and to a depth of 20–30 m
320 BC	First diving bell used by Alexander the Great
300 BC	Aristotle described the rupture of the eardrum in divers
1670	Boyle gave the first description of the decompression phenomenon as "bubble in the eye of a snake in vacuum"
1620	Cornelius Drebbel developed a one-atmosphere diving bell, basically the forerunner of all modern submarines
1691	Edmund Halley improved bell technology by devising a method to replenish air supply in the diving bell
1774	Freminet, a French scientist, reached a depth of 50 ft (2.5 ATA) and stayed there for 1 h using a helmet with compressed air pumped through a pipe from the surface
1830	Cochrane patented the concept and technique of using compressed air in tunnels and caissons to balance the pressure of water in soil
1841	Pol and Watelle of France observed that recompression relieved the symptoms of decompression sickness
1869	Publication of *Twenty Thousand Leagues under the Sea*, a science fiction novel by Jules Verne, contains a description of diving gears with air reserves
1871	Paul Bert showed that bubbles in the tissues during decompression consist mainly of nitrogen
1920	Use of gas mixtures for diving (heliox); diving depth extended to 200 m
1935	Behnke showed that nitrogen is the cause of narcosis in humans subjected to compressed air above 4 ATA
1943	Construction of aqua lung by Cousteau; diving at 200 bar possible
1967	Founding of Undersea Medical Society, USA

The Development of Hyperbaric Air Therapy

The first documented use of hyperbaric therapy actually precedes the discovery of oxygen. Landmarks in the history of hyperbaric (compressed) air therapy are shown in Table 1.2. The British physician Henshaw seems to have used compressed air for medical purposes in 1662. The chamber he developed was an airtight room called a "domicilium," in which variable climatic and pressure conditions could be produced, with pressure provided by a large pair of bellows. According to Henshaw, "In times of good health this domicilium is proposed as a good expedient to help digestion, to promote insensible respiration, to facilitate breathing and expectoration, and consequently, of excellent use for the prevention of most afflictions of the lungs." There is, however, no account of any application of Henshaw's proposed treatment, and there were no further developments in the field of hyperbaric therapy for nearly two centuries.

In the nineteenth century, there was a rebirth of interest in hyperbaric therapy in France. In 1834 Junod built a hyperbaric chamber to treat pulmonary afflictions using pressures of two to four absolute atmospheres (ATA). In 1837 Pravaz built the largest hyperbaric chamber of that time and treated patients with a variety of ailments. Fontaine developed the first mobile hyperbaric operating theater in 1877 (Fig. 1.2), and by this time hyperbaric chambers were available in all major European cities. Interestingly, there was no general rationale for hyperbaric treatments, and prescriptions therefore varied from one

Table 1.2 Landmarks in the history of hyperbaric (compressed) air therapy

1662	Henshaw used compressed air for the treatment of a variety of diseases
1834	Junod of France constructed a hyperbaric chamber and used pressures of 2–4 ATA to treat pulmonary disease
1837	Pravaz of France constructed the largest hyperbaric chamber of that time and used it to treat a variety of ailments
1837–1877	Construction of pneumatic centers in various European cities, e.g., Berlin, Amsterdam, Brussels, London, Vienna, and Milan
1860	First hyperbaric chamber on the North American continent in Oshawa, Canada
1870	Fontaine of France used the first mobile hyperbaric operating theater
1891	Corning used the first hyperbaric chamber in the USA to treat nervous disorders
1921	Cunningham (USA) used hyperbaric air to treat a variety of ailments
1925	Cunningham tank was the only functional hyperbaric chamber in the world
1928	Cunningham constructs the largest hyperbaric chamber in the world; American Medical Association condemns Cunningham's hyperbaric therapy
1937	The Cunningham chamber is dismantled for scrap metal

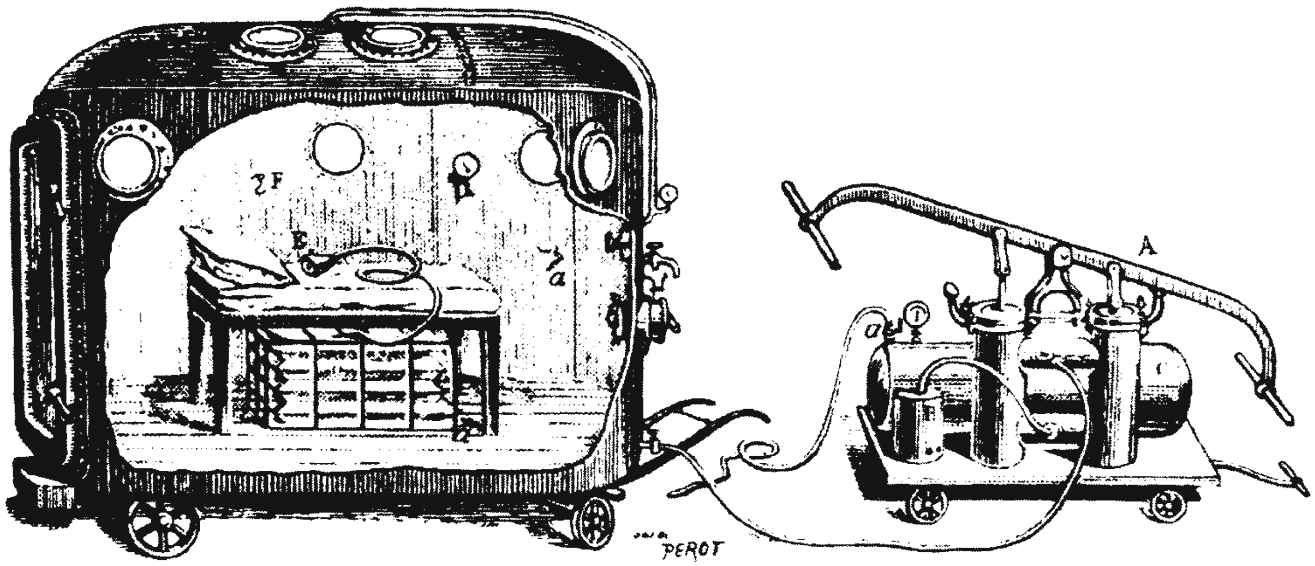

Fig. 1.2 Fontaine's mobile operating room of 1877. Note the manual nature of the compressor apparatus and the anesthesia gas container and mask in the chamber. Photo courtesy of Dr. Baixe, Toulon, France

physician to another. (In those days no methods were available to estimate the partial pressure of oxygen in blood, which at 2 ATA of air is about double that at sea level. In comparison, if pure oxygen is breathed at 2 ATA, the partial pressure of oxygen in the arterial blood is 12 times higher than normal.)

During the second half of the nineteenth century, hyperbaric centers were advertised as being comparable to health spas. Junod referred to his treatment as "le bain d'air comprimé" (the compressed-air bath). In 1855 Bertin wrote a book on this topic (the title page is shown in Fig. 1.3) and constructed his own hyperbaric chamber (Fig. 1.4).

The literature on hyperbaric medicine up to 1887 reviewed by Arntzenius contains 300 references, which is a remarkably large number for that period when publications on this topic were scarce.

The first hyperbaric chamber on the North American continent was constructed in 1860 in Oshawa, Ontario, Canada, just east of Toronto. The first such chamber in the United States was built by Corning a year later in New York to treat nervous disorders. The chamber that received the most publicity, however, and was the most actively used was that of Cunningham in Kansas City in the 1920s (Sellers 1965). He first used his chamber to treat the victims of the Spanish influenza epidemic that swept the USA during the closing days of the First World War. Cunningham had observed that mortality from this disease was higher in areas of higher elevation, and he reasoned that a barometric factor was therefore involved. Cunningham claimed to have achieved remarkable improvement in patients who were cyanotic and comatose. In 1923, the first recorded hyperbaric chamber fire occurred at Cunningham's sanatorium. He had installed open gas burners under the tank to keep it warm in winter, and someone turned the flame too high so that it scorched the interior insulation. The patients were evacuated safely. However, one night a mechanical failure resulted in a complete loss of compression and all his patients died. This tragedy was a sobering lesson but ultimately did not deter Dr. Cunningham. His enthusiasm for hyperbaric air continued, and he started to treat diseases such as syphilis, hypertension, diabetes mellitus, and cancer. His reasoning was based on the assumption that anaerobic infections play a role in the etiology of all such diseases. In 1928, in Cleveland, Cunningham constructed the largest chamber ever built—five stories high and 64 ft in diameter (Fig. 1.5). Each floor had 12 bedrooms with all the amenities of a good hotel. At that time, it was the only functioning hyperbaric chamber in the world.

As the publicity surrounding his treatments grew, Dr. Cunningham was repeatedly requested by the Bureau of Investigations of the American Medical Association (AMA) to document his claims regarding the effectiveness of hyperbaric therapy. Apart from a short article in 1927, however, Cunningham made no efforts to describe or discuss his technique in the medical literature. He was eventually censured by the AMA in 1928, in a report that stated: "Under the circumstances, it is not to be wondered that the Medical Profession looks askance at the 'tank treatment' and intimates that it seems tinctured much more strongly with economics than with scientific medicine. It is the mark of the scientist that he is ready to make available the evidence on which his claims are based."

Dr. Cunningham was given repeated opportunities to present such evidence but never did so. A more detailed account of Cunningham's story and the history of hyperbaric medicine is recorded elsewhere (Trimble 1974). The Cunningham chamber was dismantled for scrap in 1937, which brought to a temporary end the era of hyperbaric air therapy for medical disorders.

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SELON LES PROCÉDÉS

MÉDICO-PNEUMATIQUES OU D'ATMOSPHÉRIE DE M. ÉMILE TABARIÉ

PAR

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Fig. 1.3 Title page of the second edition (1868) of the book by Bertin on the treatment of diseases by compressed air

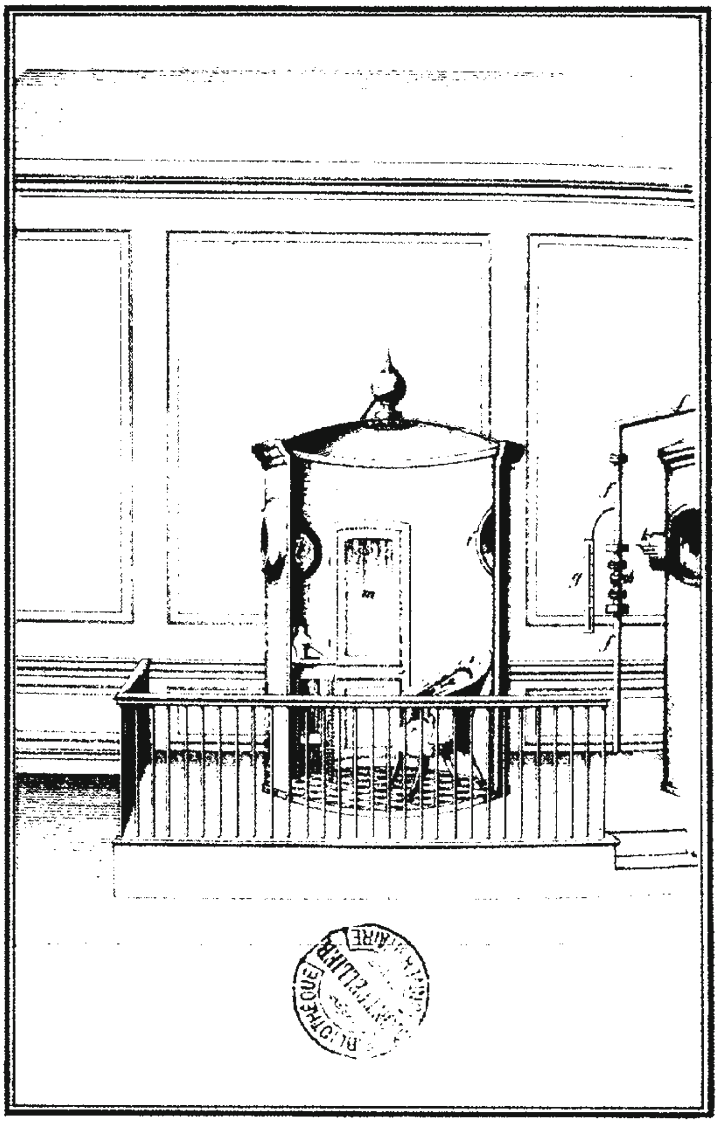

Fig. 1.4 Hyperbaric chamber constructed by Bertin in 1874

The Development of Hyperbaric Oxygen Therapy

Oxygen was not "discovered" until 1775, when the English scientist Joseph Priestley isolated what he called "dephlogisticated air." A more detailed history of the applications of oxygen since that time can be found in a book on oxygen (Jain 1989). Although hyperbaric air had been used as early as 1662, oxygen was not specifically added to early hyperbaric chambers. Landmarks in the development of hyperbaric oxygen therapy are shown in Table 1.3.

The toxic effects of concentrated oxygen reported by Lavoisier and Seguin in 1789 were reason enough for hesitation to use it under pressure. Beddoes and Watt, who wrote the first book on oxygen therapy in 1796, completely refrained from mentioning the use of oxygen under pressure. Paul Bert, the father of pressure physiology, discovered the scientific basis of oxygen toxicity in 1878 and recommended normobaric, but not hyperbaric, oxygen for decompression sickness.

The history of hyperbaric chambers is covered in two books (Haux 2000; Stewart 2011). The potential benefits of using oxygen under pressure for the treatment of decompression sickness were first realized by Dräger, who in 1917 devised a system for treating diving accidents (Fig. 1.6). For some unknown reason, however, Dräger's system never went into production. It was not until 1937—the very year that Cunningham's "air chamber" hotel was demolished—that Behnke and Shaw actually used hyperbaric oxygen for the treatment of decompression sickness. The age of hyperbaric oxygen therapy had finally arrived.

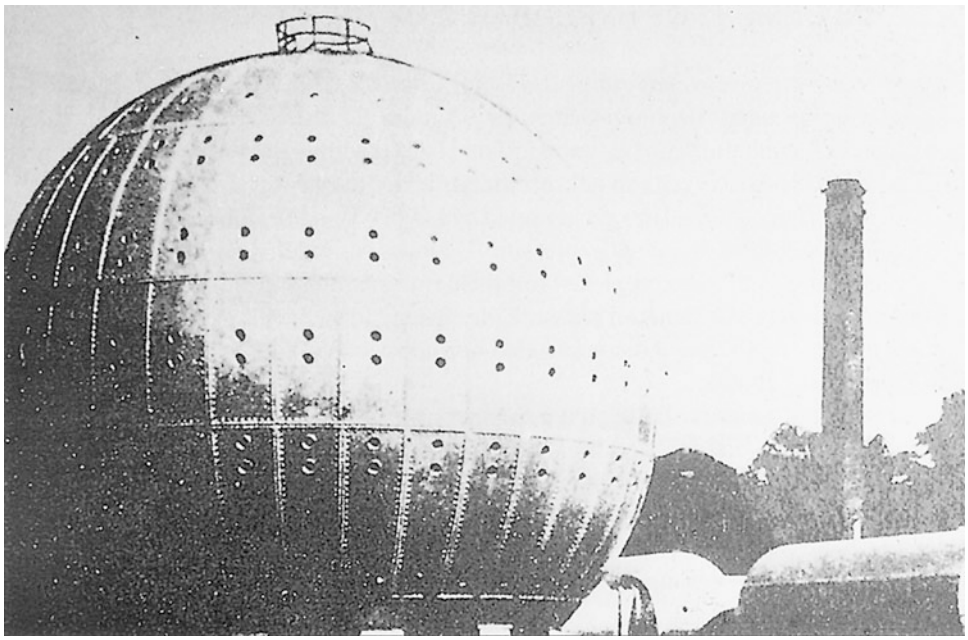

Fig. 1.5 Cunningham's giant steel ball hyperbaric chamber built in 1928 in Cleveland, Ohio. It was six stories high and contained 72 rooms. Photo courtesy of Dr. K. P. Fasecke

Table 1.3 Landmarks in the development of hyperbaric oxygen (HBO) therapy

1775	Discovery of oxygen by Priestley
1789	Toxic effects of oxygen reported by Lavoisier and Seguin: use of HBO discouraged
1796	Beddoes and Watt wrote the first book on medical applications of oxygen
1878	Bert (father of pressure physiology) placed oxygen toxicity on a scientific basis and recommended normobaric but not hyperbaric oxygen for decompression sickness
1895	Haldane showed that a mouse placed in a jar containing oxygen at 2 ATA failed to develop signs of carbon monoxide intoxication
1937	Behnke and Shaw first used HBO for treatment of decompression sickness
1938	Ozorio de Almeida and Costa (Brazil) used HBO for treatment of leprosy
1942	End and Long (USA) used HBO for treating experimental carbon monoxide poisoning in animals.
1954	Churchill-Davidson (UK) used HBO to enhance radiosensitivity of tumors
1956	Boerema (the Netherlands), father of modern hyperbaric medicine, performed cardiac surgery in a hyperbaric chamber
1960	Boerema showed life can be maintained in pigs in the absence of blood by using HBO
1960	Sharp and Smith become the first to treat human carbon monoxide poisoning by HBO
1961	Boerema and Brummelkamp used hyperbaric oxygen for treatment of gas gangrene; Smith et al. (UK) showed the protective effect of HBO in cerebral ischemia
1962	Illingworth (UK) showed the effectiveness of HBO in arterial occlusion in limbs
1963	First International Congress on Hyperbaric Medicine in Amsterdam
1965	Perrins (UK) showed the effectiveness of HBO in osteomyelitis
1966	Saltzman et al. (USA) showed the effectiveness of HBO in stroke patients
1970	Boschetty and Cernoch (Czechoslovakia) used HBO for multiple sclerosis
1971	Lamm (FRG) used HBO for treatment of sudden deafness
1973	Thurston showed that HBO reduces mortality in myocardial infarction
1970s	Extensive expansion of hyperbaric facilities in Japan and the USSR
1980s	Development of hyperbaric medicine in China
1983	Formation of the American College of Hyperbaric Medicine (founder/president, Dr. Neubauer of Florida)
1986	Undersea Medical Society (USA) adds the word hyperbaric to its name and is called UHMS. Reached a membership of 2000 in 60 countries
1987	Jain (Switzerland) demonstrated the relief of spasticity in hemiplegia due to stroke under HBO and integrated it with physical therapy
1988	Formation of the International Society of Hyperbaric Medicine

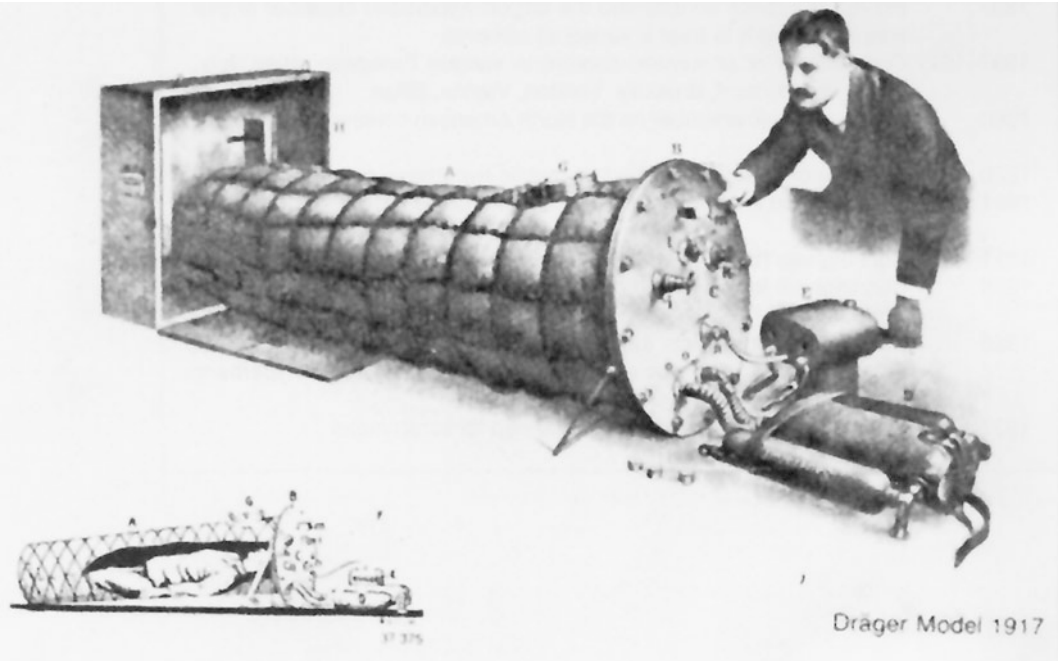

Fig. 1.6 Sketch of the 1917 Dräger 2 ATA system for diving accidents, including oxygen breathing system. Photo courtesy of Dr. Baixe, Toulon, France

References

Haux GF. History of hyperbaric chambers. Flagstaff: Best Publishing; 2000.

Jain KK. Oxygen in physiology and medicine. Springfield: Charles C. Thomas; 1989.

Sellers LM. The fallibility of Forrestian principle. Anesth Analg. 1965;44:9.

Smith EB. Priestley lecture: on the science of deep sea diving—observations of the respiration of different kinds of air. Chem Soc Rev. 1986;15:503–22.

Stewart J. Exploring the history of hyperbaric chambers, atmospheric diving suits and manned submersibles: the scientists and machinery. Bloomington: Xlibris Corporation; 2011. p. 151.

Trimble VH. The uncertain miracle—hyperbaric oxygen. New York: Doubleday; 1974.

Physical, Physiological, and Biochemical Aspects of Hyperbaric Oxygenation

2

K.K. Jain

Abstract

This chapter presents a basic scientific foundation detailing the important and interesting properties of oxygen and then surveys how these realities come into play under hyperbaric conditions. Starting with physiology of oxygenation, general effects of hyperbaric oxygenation (HBO) are described on the healthy human body. There is a specific focus on the biochemical effects of HBO and effect of HBO at molecular level. Tissue oxygen tension and biomarkers of HBO are also described. More detailed effects of HBO on various systems of the body will be described along with clinical applications in various therapeutic areas in part II of this book.

Keywords

Oxygen • Hyperbaric oxygen (HBO) • Biochemical effects of HBO • Effect of DNA on DNA • Oxygen pathway • HBO biomarker • Glucose metabolism • Ammonia metabolism • Oxygen transport • Tissue oxygen tension

Introduction

Oxygen is the most prevalent and most important element on earth. A complete and in-depth discussion of the biochemical and physiological aspects of oxygen was described in a book on oxygen (Jain 1989), and an updated brief description of how oxygen is transported and the basic physical laws governing its behavior will be useful for discussion of clinical applications of hyperbaric oxygen in the following chapters of this book. The various terms frequently encountered in relation to oxygen include:

Partial pressure of a gas	p
Partial pressure of oxygen	pO_2
Partial pressure of oxygen in alveoli	pAO_2
Partial pressure of oxygen in arterial blood	paO_2
Partial pressure of oxygen in venous blood	pvO_2

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Physical Basics

The atmosphere is a gas mixture containing by volume 20.94 % oxygen, 78.08 % nitrogen, 0.04 % CO_2, and traces of other gases. For practical purposes air is considered to be a mixture of 21 % oxygen and 79 % nitrogen. The total pressure of this mixture at sea level is 760 millimeters of mercury (mmHg). Dalton's law states that in a gas mixture, each gas exerts its pressure according to its proportion of the total volume:

$$\text{Partial pressure of a gas} = (\text{absolute pressure}) \times (\text{proportion of total volume of gas})$$

Thus, the partial pressure of oxygen (pO_2) in air is $(760) \times (21/100) = 160$ mmHg.

Pressures exerted by gases dissolved in water or body fluids are certainly different from those produced in the gaseous phase. The concentration of a gas in a fluid is determined not only by the pressure but also by the "solubility coefficient" of the gas. Henry's law formulates this as follows:

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$$\text{Concentration of a dissolved gas} = (\text{pressure}) \times (\text{solubility coefficient})$$

The solubility coefficient varies for different fluids, and it is temperature dependent, with solubility being inversely proportional to temperature. When concentration is expressed as volume of gas dissolved in each unit volume of water, and pressure is expressed in atmospheres, the solubility coefficients of the important respiratory gases at body temperature are as follows:

Oxygen: 0.024 mL O_2/mL blood atm pO_2 CO_2: 0.5 mL plasma/atm pCO_2
Nitrogen: 0.067 mL/mL plasma/atm pN_2

From this one can see that CO_2 is, remarkably, 20 times more soluble than oxygen.

Physiology of Oxygenation

The Oxygen Pathway

The oxygen pathway is shown in Fig. 2.1. It passes from the ambient air to the alveolar air and continues through the pulmonary, capillary, and venous blood to the systemic arterial and capillary blood. It then moves through the interstitial and intracellular fluids to the microscopic points of oxygen consumption in the peroxisomes, endoplasmic reticulum, and mitochondria.

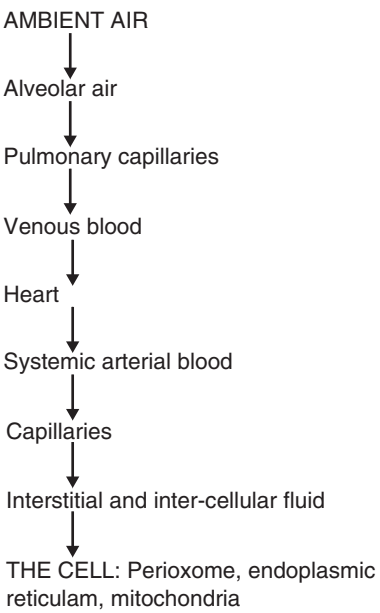

Fig. 2.1 The oxygen pathway

Ventilation Phase

Respiration, the primary goal of the lungs, is inhalation of air with uptake of O_2 contained in it, and exhalation with removal of CO_2 from the body. At rest, a normal human breathing rate is 12–15 times a minute. With each breath containing ~500 mL of air, this amounts to 6–8 L of air that is inspired and expired every minute. Once the air reaches the depths of the lung in the alveoli, simple diffusion allows O_2 to enter the blood in the pulmonary capillaries and CO_2 to enter the alveoli, from where it can be expired. On average, 250 mL of O_2 enters the body per minute, and 200 mL of CO_2 is excreted.

Oxygen is continuously absorbed into the blood as it circulates through the lungs and enters the systemic circulation. The effect of alveolar ventilation and the rate of oxygen absorption from the alveoli on the pAO_2 are both shown in Fig. 2.2. At a ventilation rate of 5 L/min and oxygen consumption of 250 mL/min, the normal operating point is at A in Fig. 2.2. The alveolar oxygen tension is maintained at 104 mmHg. During moderate exercise, the rate of alveolar ventilation increases fourfold to maintain this tension and ~1000 mL of oxygen is absorbed per minute.

Carbon dioxide is being constantly formed in the body and discharged into the alveoli by secretion is 40 mmHg. It is well known that the partial pressure of alveolar CO_2 (pCO_2) increases directly in proportion to the rate of CO_2 excretion and decreases in inverse proportion to alveolar ventilation.

Transport Phase

The difference between pAO_2 (104 mmHg) and pvO_2 (40 mmHg), which amounts to 64 mmHg, causes oxygen to diffuse into the pulmonary blood. It is then transported, mostly in combination with hemoglobin, to the tissue capillaries, where it is released for use by the cells. There the oxygen reacts with various other nutrients to form CO_2, which enters the capillaries to be transported back to the lungs.

During strenuous exercise, the body oxygen requirement may be as much as 20 times normal, yet oxygenation of the blood does not suffer, because the diffusion capacity for oxygen increases fourfold during exercise. This rise results in part from the increased number of capillaries participating, as well as dilatation of both the capillaries and the alveoli. Another factor here is that the blood normally stays in the lung capillaries about three times as long as is necessary to cause full oxygenation. Therefore, even during the shortened time of exposure on exercise, the blood can still become nearly fully saturated with oxygen.

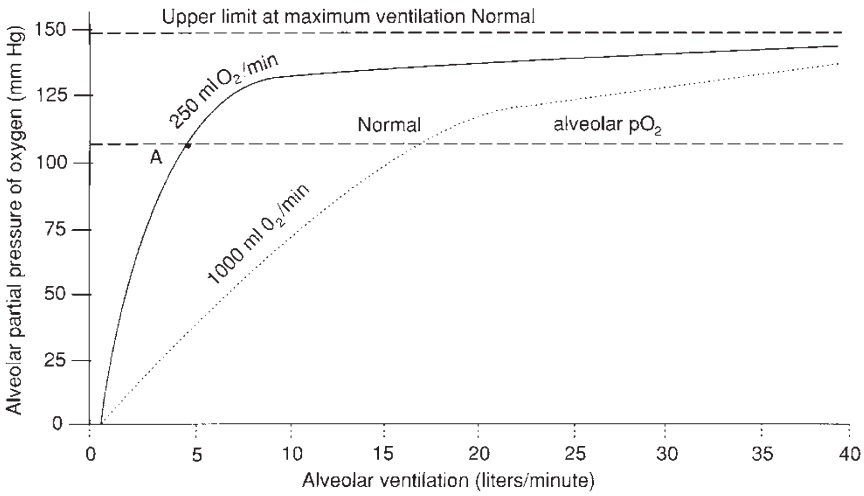

Fig. 2.2 Effect of alveolar ventilation and rate on oxygen absorption from the alveoli on the alveolar pO_2

Normally 97 % of the oxygen transported from the lungs to the tissues is carried in chemical combination with hemoglobin of red blood cells and the remaining 3 % in a dissolved state in plasma. It turns out that 1 g of hemoglobin can combine with 1.34 mL oxygen from where it is removed continuously by ventilation. The normal concentration of hemoglobin is 15 g/100 mL blood. Thus, when hemoglobin is 100 % saturated with oxygen, 100 mL blood can transport about 20 (i.e., 15 × 1.34) mL oxygen in combination with hemoglobin. Since the hemoglobin is usually only 97.5 % saturated, the oxygen carried by 100 mL blood is actually 19.5 mL. However, in passing through tissue capillaries, this amount is reduced by 14.5 mL (paO_2 40 mmHg and 75 % oxygen saturation). Thus, under normal conditions, 5 (i.e., 19.5–14.5) mL of O_2 is transported to the tissues by 100 mL blood. On strenuous exercise, which causes the interstitial fluid pO_2 to fall as low as 15 mmHg, only 4.5 mL oxygen remains bound with hemoglobin in each 100 mL blood. Thus 15 (i.e., 19.5–4.5) mL oxygen is transferred by each 100 mL blood—three times the amount transferred under normal conditions. Since cardiac output can also increase up to six or seven times, for instance, in well-trained marathon runners, the end result is a remarkable 20-fold (i.e., 15 × 6.6 = approximately 100; 100/5 = 20) increase in oxygen transport to the tissues. This is about the top limit that can be achieved.

Hemoglobin has a role in maintaining a constant pO_2 in the tissues and sets an upper limit of 40 mmHg. It usually delivers oxygen to the tissues at a rate to maintain a pO_2 of between 20 and 40 mmHg. In a pressurized chamber, pO_2 may rise tenfold, but the tissue pO_2 changes very little. The saturation of hemoglobin can rise by only 3 %, as 97 % of it is already combined with oxygen. This 3 % can be achieved at pO_2 levels of between 100 and 200 mmHg. Increasing the inspired oxygen concentration or the total pressure of inspired oxygen does not increase the hemoglobin-transported oxygen content of the blood. Thus, hemoglobin has an interesting tissue oxygen buffer function.

Shift of the Oxygen-Hemoglobin Dissociation Curve

Hemoglobin actively regulates oxygen transport through the oxygen-hemoglobin (oxyhemoglobin) dissociation curve, which describes the relation between oxygen saturation or content of hemoglobin and oxygen tension at equilibrium. There is a progressive increase in the percentage of hemoglobin that is bound with oxygen as pO_2 increases. It was first shown more than a century ago that that the dissociation curve was sigmoid-shaped (Bohr et al. 1904). This led Hill to postulate that there were multiple oxygen binding sites on the hemoglobin and to derive the following equation:

$$\left(\frac{\text{Oxygen tension}}{\text{P50}}\right)^2 = \frac{\text{Oxygen saturation}}{1-\text{Oxygen saturation}}$$

where P50 is the oxygen tension (in mmHg) when the binding sites are 50 % saturated.

Within the range of saturation between 15 and 95 %, the sigmoid shape of the curve can be described in the Hill coefficient, and its position along the oxygen tension axis can be described by P50 which is inversely related to the binding affinity of the hemoglobin for oxygen. The P50 can be estimated by measuring the oxygen saturation of blood equilibrated to different levels of oxygen tension according to standard conditions and fitting the results to a straight line in logarithmic form to solve for P50. The resulting standard P50 is normally 26.3 mmHg in adults at sea level. It is useful for detecting abnormalities in the affinity of hemoglobin for oxygen resulting from hemoglobin variants or from disease. P50 is increased to enhance oxygen unloading when the primary limitation to oxygen transport is peripheral, e.g., anemia. P50 is reduced to enhance loading when the primary limitation is in

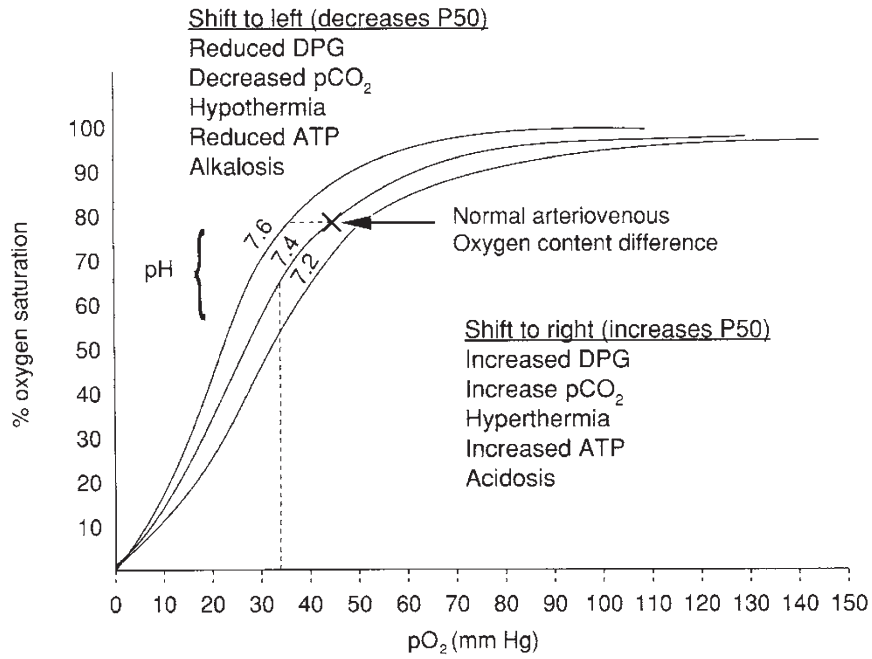

Fig. 2.3 Shift of the oxygen-hemoglobin dissociation curve. *DPG* diphosphoglycerate

the lungs, e.g., lung disease. The balance between loading and unloading is regulated by allosteric control of the P50 and chemoreceptor control of ventilation which is matched to diffusing capacities of the lungs and the tissues. Optimal P50 supports the highest rate of oxygen transport in health and disease.

A number of conditions can displace the oxyhemoglobin dissociation curve to the right or the left, as indicated in Fig. 2.3.

Delivery of Oxygen to the Tissues

During transit from the ambient air to the cellular structures, the pO_2 of oxygen drops from 160 mmHg to a few mmHg in the mitochondria. This gradual drop is described as the "oxygen cascade" and is shown in Fig. 2.4.

Oxygen Transfer at the Capillary Level

There is considerable resistance to oxygen transfer in the capillaries, and this is as significant as the resistance in the surrounding tissues.

Microvascular geometry and capillary blood flow are the most important factors responsible for regulating the oxygen supply to the tissues to meet the specific oxygen demands of organs such as the heart and brain. The tissues, of course, form the end point of the oxygen pathway. The task of the active transport system is to ensure an adequate end-capillary pO_2 so that passive diffusion of oxygen to the mitochondria is maintained.

Relation Between the Oxygen Transport and Utilization

The relationship between the transportation of oxygen and its utilization was first described long ago by Fick (1870). According to the Fick principle, oxygen consumption of the tissues (pO_2) is equal to the blood flow to the tissues (Q), multiplied by the amount of oxygen extracted by the tissue, which is the difference between the arterial and the mixed venous oxygen contents, $C(a-v)O_2$:

$$\text{Oxygen Consumption}\left(VO_2\right) = \left(Q\right)\times\left(C\left(a-v\right)O_2\right)$$

As the VO_2 of a given tissue increases, the normal response in the human body is to increase the local blood flow to the area, to maintain the local $(a-v)O_2$ content difference close to the normal range. A marked increase of $(a-v)O_2$, above 4–5 vol.%, is observed during physical exercise, as discussed further in Chap. 5. An increase of this magnitude in non-exercising individuals usually means an impaired circulation, inadequate to meet the increased demand of the tissues in some disease states, or it means that the oxygen content of the arterial blood is very low. The increased extraction of oxygen from the blood leads to a lower pO_2 compared to the normal level of 35–40 mmHg with O_2 saturation at 75 %. Naturally the regional flow throughout the body is variable, and organs such as the heart and brain extract much more oxygen from the blood than do other organs. The brain makes up 2–3 % of body weight but receives 15 % of the cardiac output and 20 % of the oxygen

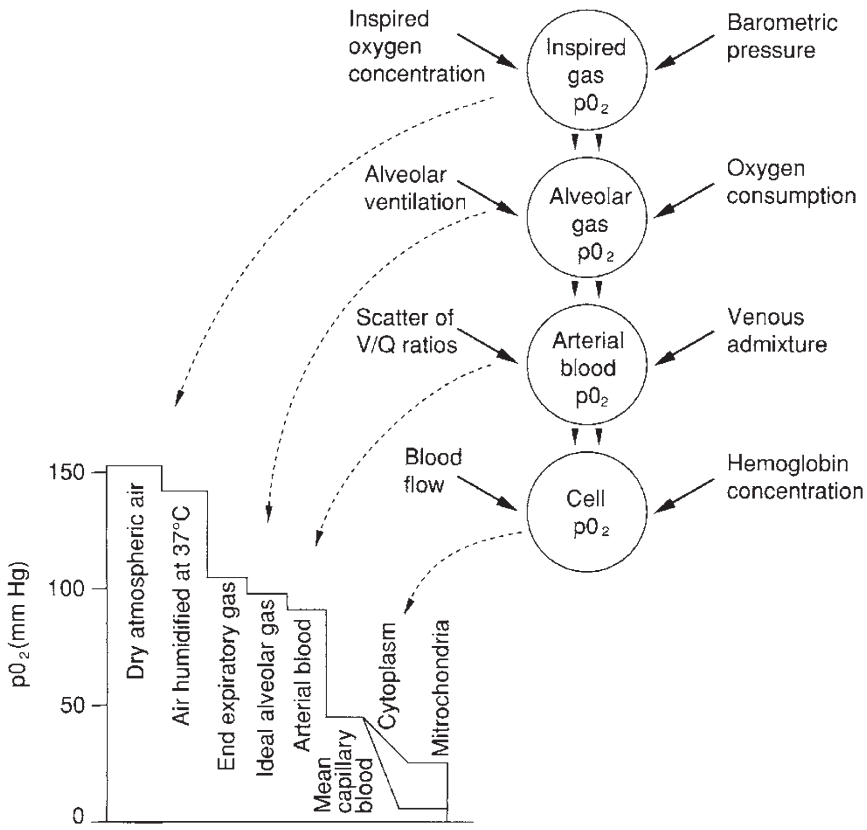

Fig. 2.4 The oxygen cascade

uptake of the entire body. Within the brain, cerebral blood flow and oxygen uptake vary according to the level of cerebral activity.

Oxygen Utilization in the Cell

The major site of utilization of molecular oxygen within the average cell is the mitochondria, which account for about 80 %, while 20 % is used by other subcellular organs, such as the microsomes, nucleus, plasma membrane, etc. Oxygen combines with electrons derived from various substrates to release free energy. This energy is used to pump H+ ions from the inside to the outside of the mitochondria against an electrochemical gradient. As H+ ions diffuse back, free energy is made available to phosphorylate adenosine diphosphate (ADP), and adenosine triphosphate (ATP) is generated.

Only a minute amount of oxygen is required for the normal intracellular chemical reactions to take place. The respiratory enzyme system is so geared that when tissue pO_2 is more than 1–3 mmHg, oxygen availability is no longer a limiting factor in the rate of chemical reactions. Under normal conditions, the rate of oxygen utilization by cells is controlled by the rate of energy expenditure within the cells, i.e., by the rate at which ADP is formed from ATP.

The diffusion distance from the capillary wall to the cell is rarely more than 50 μm, and normally oxygen can reach the cell quite readily. But, if pO_2 falls below the critical value of 1–3 mmHg, and if the cells are located farther away from the capillaries, the oxygen utilization is diffusion limited and not determined by ADP. This is particularly true for cerebral white matter, which is very sensitive to hypoxia as well as hyperoxia.

Effect of Blood Flow

Since oxygen is transported to the tissues in the bloodstream, interruption of blood flow means that the amount of available oxygen to the cells also falls to zero. Under these conditions, the rate of tissue utilization of oxygen is limited by blood flow.

Effect of Oxygen-Hemoglobin Reaction on Transport of CO_2

This response, known as the Haldane effect, results from the fact that combination of oxygen with hemoglobin causes it to become a stronger acid. This displaces CO_2 from the blood in two ways: