Chemical Oxygen Generation

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Summary

While pressurized oxygen in tank form, as well as oxygen concentrators, are ubiquitous in civilian healthcare in developed countries for medical use, there are a number of settings where use of these oxygen delivery platforms is problematic. These settings include but are not limited to combat casualty care and healthcare provided in extreme rural environments in undeveloped countries. Furthermore, there are a number of settings where delivery of oxygen other than the pulmonary route to oxygenate tissues would be of value, including severe lung injury, airway obstruction, and others. This paper provides a brief overview of the previous and current attempts to utilize chemical oxygen production strategies to enhance systemic oxygenation. While promising, the routine use of chemically produced oxygen continues to pose significant engineering and physiologic challenges.
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Introduction

Oxygen is essential for life, having its main role at the cellular level, where it is used by the mitochondria during oxidative phosphorylation to produce adenosine triphosphate, which is essential for the myriad of metabolic processes that keep us alive. While a bit elementary, the rudimentary formula for oxygen delivery is:

$$DO_2 = \text{cardiac output} \times \text{arterial oxygen content}$$

where DO_2 is oxygen delivery.[1]

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Arterial oxygen content = (1.36 × hemoglobin in g/dL × S_{aO_2}) + (P_{aO_2} × 0.003)

where S_{aO_2} is arterial hemoglobin oxygen saturation percentage and P_{aO_2} is partial pressure of oxygen dissolved in plasma.[1]

While this is the formula for whole body delivery, the same equations could easily be written for each individual organ. As can be noted by the formula, there are a number of ways in which tissue hypoxia can result. These include decreases in critical flow, such as a reduction in cardiac output; hypoxic hypoxia, such as during asphyxia (which results in critical decreases in hemoglobin oxygen saturation); and reductions in hemoglobin, such as might occur during hemorrhage.

Despite its etiology, lack of oxygen for this process of aerobic metabolism can have catastrophic effects, leading to accumulation of oxygen debt, multisystem organ failure, and death.[2] When vital levels of oxygen are lacking in a particular organ such as the heart or brain, below which aerobic metabolism cannot be maintained, we term it as a myocardial infarction or stroke, respectively. When this occurs in multiple organs in close succession, we term it shock. Of course, the above explanation is oversimplified and does not take into account the complexities of the microcirculation, which include inflammation and other important regional and global processes.[3,4] It also, for the time being, ignores the importance of oxygen as a cell signaling molecule that is capable of setting into play a number of either helpful or injurious processes.[5–7] While the amount of oxygen dissolved in plasma negligibly contributes to total DO_2, through the equation above, there will be an equilibrium between plasma P_{O_2} and S_{aO_2}. Furthermore, as discussed in other reviews in this issue, there may be evidence that increasing P_{aO_2} is tissue sparing or tissue damaging in some settings. Thus, the P_{aO_2} level in the setting of critical illness and injury cannot simply be dismissed.

In general, however, use of supplemental oxygen during ventilation is viewed as helpful in the setting of acute critical illness and injury, as a means to prevent overt hypoxemia and to ensure adequate hemoglobin oxygen saturation. Our main tool for ensuring this is the use of pressurized oxygen systems, either in portable gas tank form or from the transition of liquid oxygen stores to pressurized gas stores, as occurs in hospital systems.[8]

While convenient for the most part for day-to-day use, there are a number of settings where our conventional use of oxygen in this setting does not meet our needs. These include:

- Use of oxygen in emergencies in austere environments. Examples of this would include undeveloped countries, especially in the rural setting, where the availability of pressurized oxygen tanks is poor and rapid replacement of tanks is not possible or practical. In combat zones, for example, pressurized oxygen tanks represent extreme explosive hazards and their weight poses substantial challenges to the mission. While the development of ceramic oxygen generators is promising, the battery life and need for supplemental power pose additional challenges in these environments. Although the value of supplemental oxygen in trauma, especially in combat, has been debated, mounting evidence suggests that it is of substantial value, especially in the setting of deliberate hypotensive resuscitation and in the setting of blast injury.[9,10]
- Use of oxygen in settings where ventilation cannot adequately be performed or in which there is a specific need to supplement oxygen availability to specific organ systems. Examples of this would include severe lung injury or airway obstruction. In these settings, supplemental oxygen delivered conventionally by inhalation is inadequate to prevent deterioration. Additionally, situations where organs are vascularly compromised, such as the intestinal beds or wound beds, may see little or no elevations in critical oxygen delivery suitable to prevent additional injury. The same might be said of organs such as the heart and brain.

For these and other reasons, there has been a longstanding interest in alternative means to provide systemic and local tissue oxygen support.

Chemically Produced Oxygen

Chemical oxygen production and delivery, in several forms, has been experimented with since the early 1900s. By chemical we mean to say that the oxygen is stored in a form other than gaseous diatomic oxygen. Gaseous oxygen is produced from such storage materials via chemical reaction.

Perhaps the best known and most frequently observed example of chemically bound but available oxygen is hydrogen peroxide (H_2O_2). H_2O_2 is a commonly available oxidizer used in the medical and food industries as a disinfectant. H_2O_2 is also produced as a metabolic product by the body, as a reactive oxygen species.[5,11] The molecule has important roles in cell signaling, but can also have harmful cellular effects at inappropriate concentrations.[11]

H_2O_2 decomposes exothermically to water and oxygen gas by the following stoichiometry:

$$2H_2O_2 \rightarrow 2H_2O + O_2$$

This reaction occurs spontaneously but slowly over time. The addition of a catalyst (eg, catalase, peroxidases, man-

ganese dioxide, iron, and many others) will substantially accelerate the reaction. Catalysis by catalase is commonly observed when H_2O_2 is applied to a wound. The fizzing and bubbling that results is due to the catalytically enhanced rate release of oxygen from the decomposition of the H_2O_2. The human body has one of the most abundant levels of catalase in the animal kingdom, a level likely related to the need to rapidly catalytically destroy H_2O_2 that is produced by metabolism to prevent substantial cellular damage.[12,13]

As an example of how much oxygen the reaction above produces, 1 mL of 3% H_2O_2 (over the counter from the drug store) will produce 11.4 mL of oxygen at 37°C and 1 atmosphere in seconds when exposed to biologic concentrations of catalase. This fundamental reaction has prompted experimentation for close to a century in the use of liquid H_2O_2 of various concentrations for intravenous delivery, to produce systemic and local oxygenation.

The fundamental challenge in this approach is to control the release of oxygen that is produced by the reaction. Oxygen is soluble in plasma to only ~3 mL/L of blood. Thus, as noted above, 1 mL of 3% H_2O_2 fully reacted would rapidly saturate almost 4 L of plasma, and 2 mL nearly 8 L, essentially producing hyperbaric amounts of oxygen. As such, production of oxygen in plasma at a rate that exceeds the rate of consumption by surrounding tissues will result in gas emboli created when excess oxygen comes out of solution. As an example of how quickly oxygen can form, multiple case reports exist of severe complications and fatalities from oxygen emboli after accidental oral ingestion or application of 3−35% H_2O_2.[14–18] In these cases it is likely that H_2O_2 is rapidly converted by catalase in the lumen of the intestines or from blood at the application site. In the case of ingestion, oxygen produced at this rapid rate and quantity (depending on the amount of H_2O_2 ingested) cannot be readily metabolized by the intestinal villi nor transit the entire intestinal bed leaving as flatulence. As a result, some of the oxygen necessarily traverses vascular plexi in the intestines and enters the systemic circulation as venous and arterial emboli. This, in turn, has resulted in stroke, pulmonary emboli, cardiac arrest, and other complications. In fact, reports exist of arterial emboli from 3% H_2O_2 after using it to irrigate wounds.[16,17]

It is remarkable then to study the reports of H_2O_2 used in animals and humans to treat various ailments. These include the delivery of various concentrations of H_2O_2 via different routes (intravenous, intra-arterial, rectally, et cetera) to provide systemic and regional oxygenation in a variety of settings, ranging from systemic hypoxemia due to influenza, cardiac arrest, or regional wound care, and as a means to hypersensitize various tumors to radiation therapy.[19–48] While reports exist of remarkable success, the technique appears to be largely abandoned by the medical community, due to the production of gas emboli. Despite this, H_2O_2 therapy is available in various forms from the nutraceutical industry, including options of intravenous use, which can be purchased via the Internet.

Current Examples of Chemical Oxygen Generation

A little appreciated but ubiquitous application of chemical oxygen generation exists in the airline industry. Commercial aircraft are equipped with chemical oxygen generators (COGs) to provide emergency oxygen to passengers in the event of sudden loss of cabin pressure. These systems are housed either above the passenger or in the backrest of the seat in front of the passenger. The systems typically utilize the decomposition of a mixture of chlorates, perchlorates, and sometimes superoxides. The sodium chlorates ($NaClO_3$) and sodium perchlorates ($NaClO_4$) decompose exothermically above 400°C to produce oxygen and salt (NaCl), with the reaction temperature being maintained by the release of heat during the decomposition. The dry chemicals are reacted by an initial burst of heat provided by an explosive cap containing a mixture of lead styphanate and tetrazene, for example. Oxygen is produced at a constant rate for 15–20 min, with the rate mitigated and controlled by a variety of other additives (eg, metal oxides and hydroxides) and inert diluents (glass powder). $Ca(OH)_2$, for example, decomposes endothermically around 400–500°C to produce CaO and water; addition of this hydroxide can be used to limit the internal temperature increase of the device.

The chemical mixtures in these devices can be stored almost indefinitely at both cold and hot temperatures: a distinct advantage for inventory control and military use. Unhappily, the reaction is extremely exothermic and the interior temperature can reach 600°C. Despite the obvious implications of the high temperatures, these candles continue to be used on all commercial aircraft. While there has never been a single documented instance in which these devices have saved a life, they have been responsible for explosions, including ValuJet flight 592 (expired generator shipped improperly) and aboard the nuclear-powered submarine HMS Tireless. All oxygen candles produce oxygen with highly exothermic reactions, and all exhibit very high internal temperatures. They are, for obvious safety reasons, problematic for widespread domestic or clinical use. The devices also have restrictions regarding shipping.

Potassium superoxide (KO_2) is used in the mining industry in rescue breathing systems. KO_2 reacts exothermically with water in the exhaled air of a user to produce KOH and oxygen. The KOH is used in a clever recirculation design to absorb CO_2 in the exhaled air at the same time the air is replenished with oxygen.

$$4KO_2 + 2H_2O \rightarrow 4KOH + 3O_2$$

$$2KOH + CO_2 \rightarrow K_2CO_3 + H_2O$$

$$K_2CO_3 + CO_2 + H_2O \rightarrow 2KHCO_3$$

The rebreathing circuit must also include a heat exchanger to cool the circulating air, since it is constantly being heated by the exothermic reaction. Unfortunately, if KO_2 is overtly reacted with enough water, the reaction is explosive. The by-product, potassium hydroxide, is a very strong caustic and can cause serious chemical burns to the skin and especially to the eyes. Therefore, disposal or recycling of KO_2 canisters is challenging and must be done professionally. The canisters are an unacceptable environmental hazard if land-filled, since leaching of KOH from these devices is a very active aquatic toxin. Thus, for both safety and environmental disposal reasons, these systems are also likely to be unsuitable for widespread domestic or hospital use.

Newer Evolution to Older Approaches

Chemical Oxygen Generators

While the mainstay of chemical oxygen generation for individual use has resided in the airline and mining industries, as outlined above, there has been a desire to revise or re-engineer various facets of stored oxygen chemistry and hardware design to produce small, portable, lightweight, and safe chemical oxygen generators (COGs). COGs could be envisioned to have value where a system is desired to be totally disposable or rechargeable, and where access to electrical power (even batteries) is not possible or practical. Such settings include remote casualty care field and rural care and clinics in poorly developed countries. However, the F_{IO_2} and oxygen delivery time required from such devices, as well as other mission specific details, would inherently dictate the design of portable COGs. For example, for military purposes, size and weight are of utmost concern, and these dictate limits on the amount of oxygen a chemical device might generate. For any over the counter use for civilians, safety will also be a major concern. The FDA (21 Code of Federal Regulations 868.5440) dictates that, in order to be considered for over the counter use, a COG must provide a minimum of 6 L of oxygen flow for a minimum of 15 min. While such output may have utility for emergency use in developed countries in which additional oxygen will be quickly forthcoming, such devices would have little utility in remote settings where access to additional oxygen or emergency care will be delayed. Of course, the F_{IO_2} provided at a flow rate of 6 L/min will depend on several important factors, including how it is delivered (type of mask, nasal cannula, etc) and the respiratory pattern of the subject, including minute ventilation. Lower flow rates are capable of providing higher than expected F_{IO_2} values with the use of special face masks.[49] With that in mind, all of the chemistries and devices described can produce medically breathable oxygen, albeit at different rates and time spans.

Three main options exist for creation of COGs. These include:

- Adaption of candle technology, as described earlier. The chemistry utilized for "candle" production of oxygen probably offers the best value in terms of amount of oxygen produce per weight of product. For example, sodium chlorate ($NaClO_3$) is a bit more than 22.5 weight % O_2, and sodium perchlorate ($NaClO_4$) contains 26.1 weight % O_2. The amount and rate of flow is dictated by the amount of material used and its molded shape, which dictates in many respects how fast the material burns. It has an additional advantage in that it is probably has no storage lifetime or environmental storage limitations other than dryness. However, as indicated above, the burning that is required to produce oxygen through thermal decomposition is highly exothermic (reaching 400–600°C) and reaction vessels of any sort require substantial insulation to prevent skin contact and burns, perhaps making it widely available to civilians problematic. The FDA standard mandates surface temperatures < 45°C. It is also not clear how prolonged oxygen production can be with controlled rates.
- Adaptation of potassium superoxide technology, as described earlier. As discussed earlier, the KO_2 chemistry used in the mining industry, while appearing ideal (oxygen production and carbon dioxide consumption), requires water vapor to initiate and maintain the reaction. This of course would require a subject to have spontaneous respirations to a degree that would allow filling of the device's circuit. No reports exist of the technology being adapted for use during mechanical ventilation. While the technology has a favorable weight and size footprint, it would require engineering that prevented any exposure of the system to more water than exists in human breath, as the combination of chemistry is explosive in contact with liquid water. Additionally, the disposal difficulties and safety issues noted earlier are substantial. Similar to candle chemistry, KO_2 (22.5 weight % O_2) has favorable oxygen content and storage requirements.
- Use of peroxide species. As discussed earlier, hydrogen peroxide (47.1 weight % O_2 yield) is easily decomposed to produce oxygen. Liquid peroxides are fairly temperature sensitive and can undergo substantial degradation. In addition, concentrations become increasingly more irritating to the skin at concentrations above 20%.

However, several solid forms of hydrogen peroxide exist, including sodium percarbonate and urea hydrogen peroxide. Sodium percarbonate is a solid adduct of sodium carbonate and hydrogen peroxide ($2Na_2CO_3 \cdot 3H_2O_2$). When exposed to water, it produces sodium carbonate and hydrogen peroxide as follows:

$$2Na_2CO_3 \cdot 3H_2O_2 \rightarrow 2Na_2CO_3 + 3H_2O_2$$

In pure form, sodium percarbonate can deliver 15.3 weight % O_2, but readily available "high purity" grades (produced in bulk for laundry soap products) typically contain about 85 weight % percarbonate, 15 weight % sodium carbonate, and 1.5 weight % sodium silicate.

As with all peroxide-releasing adducts, the rate of oxygen production from sodium percarbonate can be increased by the addition of catalysts. Sodium percarbonate is resistant to auto-oxidation and degradation, and thus offers an advantage of being easily stored and used at higher environmental temperatures than urea hydrogen peroxide. The production of oxygen from sodium percarbonate is always accompanied by a great deal of foaming, which, while perhaps useful for detergents, must be greatly mitigated or eliminated if the oxygen is to be used for breathing, lest the gas flow is unexpectedly contaminated with the foam. Unfortunately, most commercial antifoaming agents, even if found to be effective for percarbonate foam, cannot be used, due to the presence of volatile organics in the antifoam formulations. Mechanical structures such as mesh can be utilized as foam breaking strategies.

Another readily available solid peroxide species is urea-hydrogen peroxide (UHP) or percarbamide peroxide ($CH_6N_2O_3$). UHP is available in purities approaching 98% and can deliver 17.0 weight % O_2. UHP is used as an oxidizer and disinfectant in the cosmetic and pharmaceutical industry, and, along with percarbonate, often appears in teeth whitening formulations. When contacted with water, UHP instantly separates into urea and H_2O_2. The hydrogen peroxide is then available to decompose to oxygen and water, and its rate of decomposition can be accelerated by various catalysts. Generally, UHP produces oxygen from aqueous solutions with far less foaming than percarbonate, but the UHP adduct becomes unstable as the storage temperature approaches 40°C. The adduct breaks down in just a few hours at 50°C. The decomposition at 40°C can be slowed substantially, but not eliminated by the addition of 2 weight % caffeine. UHP is also moderately hygroscopic and must be stored in air-tight containers. The oxygen yield from UHP is substantial, with an oxygen delivery equivalence of 0.831 g UHP/g 30% H_2O_2. That is, UHP delivers 17.01 weight % O_2, while 30% peroxide solution yields 14.1 weight % O_2. Thus, the transport and storage of UHP carry concerns similar to those associated with the transport and storage of 30% hydrogen peroxide.

Both of these solid peroxide species can take the form of free flowing powders, and, while essentially harmless, UHP and percarbonate can, if held for several minutes, cause subcutaneous hydrogen peroxide burning sensations typical of contact with 30 weight % hydrogen peroxide solutions. The stinging is caused by the release and absorption of peroxide into the skin and subcutaneous reaction with catalase.

Two current COGs are cleared by the FDA. One utilizes sodium percarbonate and one utilizes UHP. In general, both offer similar advantages and disadvantages over the other chemistries described. The amount and rate of oxygen produced are generally determined by the amount of the peroxide species used. If reacted freely, both reactions are also exothermic to a degree that could be hazardous. Mitigation of the heat produced is possible either through insulation, the use of additional water, or the use of additional chemistries, which absorb some of the heat produced. Thus, if not carefully designed either from a mechanical housing or chemical engineering aspect, the above peroxide reactions could run unchecked, producing dangerous levels of heat and even poisoning the catalyst, causing the reaction to stop.

Unfortunately, the engineering factors required to safely control the reaction and produce sufficient oxygen flows come with a weight and size cost that are above those of the candle and KOH technologies. We have taken a novel approach of pressing 23 mm diameter tablets made from these peroxide species. These large tablets dissolve slowly in a catalyst-containing aqueous reaction mixture, similar to the dissolution of a throat lozenge in the mouth, and present a reasonably constant surface area during the reaction. The slowdown in rate that would otherwise accompany the eventual loss of surface is offset by controllably ramping the temperature, which increases the rate. This strategy allows for a high level of precision in the release and reaction of the H_2O_2 to the point that near zero order release of oxygen is possible for the duration of the device's use. It is possible to produce nearly constant flows, ranging form 250 mL/min to 6 L/min for 2 or more hours to about 20 min, respectively.

When hydrogen peroxide decomposes to water and oxygen, the reaction releases 46,880 cal/mol O_2 or about 1.94 cal/mL breathable oxygen. To put this in perspective, a device engineered to produce 60 L of breathable oxygen will release about 116,280 cal, while only 78,000 calories are required to raise the 1,100 g of aqueous solution used in the device to 100°C (boiling point). The energy release is balanced by using the dissolution of solid urea (58 cal/g endothermic) to absorb about a third of the heat generated, another third is transferred by conduction/convection to the air around the device, and the remaining third is used to slowly heat the contents to about 50°C, in order to maintain the oxygen delivery rate as the tablets dissolve.

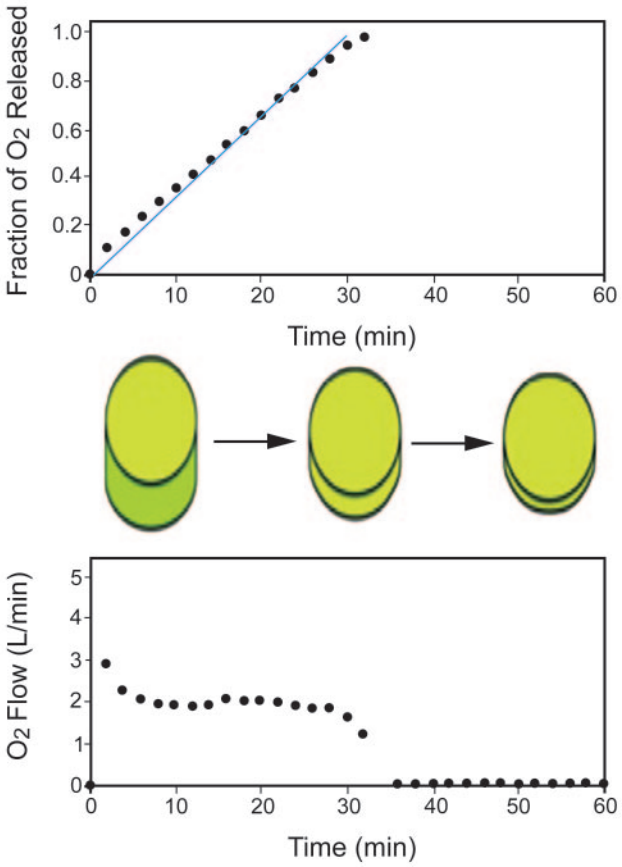

Fig. 1. Lozenge type tablet creation of urea-hydrogen peroxide, allowing for slow dissolution and production of oxygen. The solid line in the upper graph represents perfect zero order production of oxygen. The dotted line in the upper graph demonstrates real-time production of oxygen close to zero order kinetics. The lower graph demonstrates constant production of 2 L/min oxygen for 30 min.

Because the solubility of urea increases linearly with temperature, the amount of cooling from urea dissolution increases as the device temperature rises. Likewise, the rate of heat transfer to the surroundings increases as the internal temperature rises and the thermal gradient to the outside increases. These 2 phenomena, combined with the controlled availability of UHP due to the tablets, makes the device inherently safe—the reaction cannot "run away" thermally. Figure 1 illustrates the approach and kinetics of the chemical engineering behind the design. We measure the release of oxygen gravimetrically and numerically differentiate the data to determine a volumetric flow rate. For the amount of UHP used in a 60 L device, an almost zero order rate of O_2 is released for a 2 L/min version, resulting in a constant 2 L/min flow for 30 min. The maximum internal temperature of this device is about 50°C. Again, various formulations can be produced, which create almost any desired flow rate.

If used with rebreathing circuits, and assuming an oxygen consumption of 400–500 mL/min, similar systems can be designed to deliver an F_{IO_2} of 0.5 or greater for 2 hours at the same weight required to produce 6 L/min for 15 min. Such systems could even be envisioned to be used to supply supplemental oxygen to patients undergoing mechanical ventilation. The need to consider these types of approaches may be necessary in the event of pandemics such as avian flu, where use of mechanical ventilation without supplemental oxygen may have limited utility, and when ventilator use of such magnitude may overwhelm a hospital's usual ability to supply oxygen.[8,50] There is little appreciation for the volume of oxygen used in typical healthcare settings.[8,51,52] Large liquid oxygen storage tanks used by hospitals deliver oxygen through copper piping at 50 psi. Supplying 4 L/min of oxygen to 100 patients would utilize 576,000 L of oxygen per day. The typical large H cylinder contains approximately 7,000 L of oxygen.

Alternative Chemical Delivery Methods

Splanchnic Oxygenation

As indicated earlier, attempts to provide systemic oxygenation with H_2O_2 have been tested by infusing H_2O_2 into the intestines, including the large bowel.[45,46] However, this approach has not been further developed, or at least reported, because of issues of oxygen emboli development due to the uncontrolled production of large amounts of oxygen.

While it may be impractical to provide substantial systemic oxygenation via intraluminal bowel oxygenation, the use of intraluminal bowel oxygenation may have other important benefits. The splanchnic bed (liver and intestines) accounts for over one third of the body's oxygen utilization.[53–55] The intestines are at particular risk, due to the countercurrent blood supply to the intestinal villi. This vascular architecture makes the villi especially prone to ischemia, resulting in translocation of intestinal mediators into the systemic circulation.[54] Splanchnic bed tissue hypoxia (from hemorrhage, infection, hypoxemia, or ischemia from abdominal compartment syndrome) is believed to be the major cause of sepsis and multisystem organ failure.[53–57] The advent of damage control surgery has resulted in an increased incidence of abdominal compartment syndrome, further placing the splanchnic bed at risk.[58]

The intraluminal microvascular surface area is immense and matched only by that of the lung. By providing an intraluminal source of oxygen to the villi and its vasculature, it should be possible to spare the intestines and even the liver (which receives half of its blood supply by the portal vein emptying the intestines) from severe tissue hypoxia. Intraluminal oxygenation has been shown to sig-

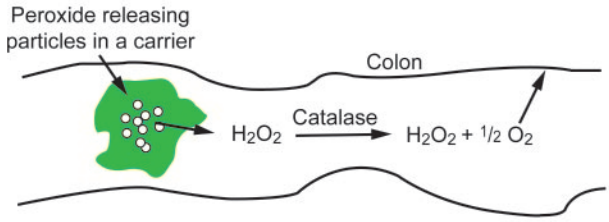

Fig. 2. Representation of sustained release strategy of intestinal H_2O_2 delivery and oxygen production vehicle.

nificantly decrease intestinal permeability and necrosis from ischemia.[53,54,56,57,59–65]

Instillation of simple gaseous oxygen would seem to be an easy solution, but presents delivery challenges in terms of developing an apparatus for precise delivery and ensuring delivery through all parts of the intestines. Simply dripping H_2O_2 into the intestines, which also would appear to be easy, will likely produce too much O_2 in the proximal portions (or large bowel if delivered rectally). A potentially better strategy may be to develop an H_2O_2 delivery system that will allow for a controlled release of O_2 as the H_2O_2 traverses the length of the intestines (Fig. 2).

We have produced several early prototype methods to control for the release of H_2O_2. One such system utilizes mesoporous silica particles, which exhibit low densities and high surface areas, as a result of the network of well defined nano-channels that emanate from the core to the outer surface of the particles. In recent years, extensive efforts have been dedicated to incorporating drugs in mesoporous silica to achieve controlled delivery rates. Some of the drugs successfully loaded into silica particles include ibuprofen and others.[66] In this example silica particles are loaded with 20–30 weight % H_2O_2. To mitigate the release rate of H_2O_2, palmitic acid is tethered to the surface of the free flowing silica particles and then suspended in olive oil with SPAN 80 to create a stable emulsion. In both cases the polar H_2O_2-rich particles are surrounded by non-polar alkyl tails and non-polar oil that acts as a barrier for the release of H_2O_2, since the solubility of H_2O_2 in a non-polar phase is very low (Fig. 3).

Figure 4 shows the temporal evolution of O_2 from the H_2O_2 that has diffused from loaded silica particles. The general idea is to provide a slow release of H_2O_2 and thus continuous oxygen as the mixture makes its way through the gastrointestinal tract. We have tested this approach in animals (swine) made systemically hypoxemic by reducing the F_{IO_2} from 0.21 to 0.1 to 0.07. Figure 5 demonstrates the intestinal wall P_{O_2} levels, systemic P_{O_2}, and mixed venous oxygen saturation in animals at baseline, during hypoxemia, and during hypoxemia after receiving a single intestinal 150 mL bolus of the H_2O_2 silica particle emulsion. Measurements of the serosal intestinal wall P_{O_2} levels over the length of the small and large bowel showed

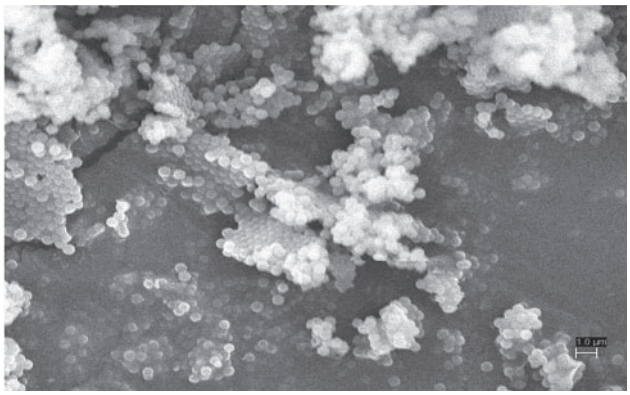

Fig. 3. Scanning electron micrographs of H_2O_2 loaded mesoporous silica particles tethered with palmitic acid. Silica particles are $\leq 1\ \mu m$ with pore sizes between 2–5 nm. Once loaded, the particles are 30% by weight H_2O_2.

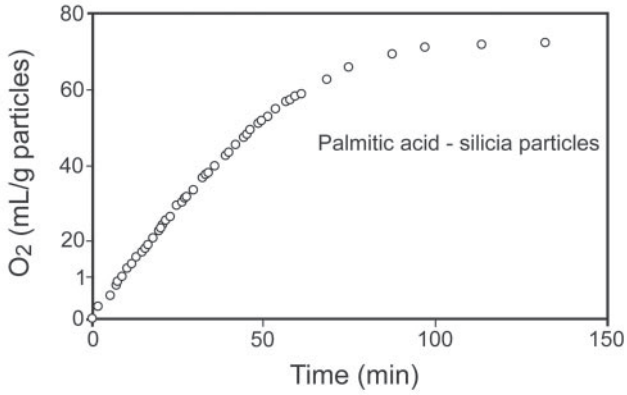

Fig. 4. Release profile of H_2O_2 loaded mesoporous silica particles tethered with palmitic acid and emulsified in olive oil, demonstrating delayed and prolonged release in a water solution saturated with catalase.

return of P_{O_2} levels above critical ischemic levels. The intraluminal P_{O_2} levels should be substantially higher. While not shown, liver P_{O_2} levels were also elevated above ischemic levels, indicating oxygen uptake from the portal vein. While mixed venous oxygen saturations and P_{aO_2} levels were not elevated, it may be possible to do this with higher concentrations of loaded particles. The results, at the very least, indicate the strategy may be one that benefits operative and postoperative patients, and may reduce splanchnic ischemia leading to multi-organ failure. No evidence of systemic toxicity was evident, and the intestinal pressures did not exceed 10 cm H_2O.

Use of such strategies overcomes the inherent limitations of blood flow (cardiac output or regional flow) as a part of the DO_2 equation above. By supporting an organ system, such as the splanchnic bed in this case, it may be possible to enhance systemic recovery while avoiding additional organ failure. If provided with enough oxygen, it

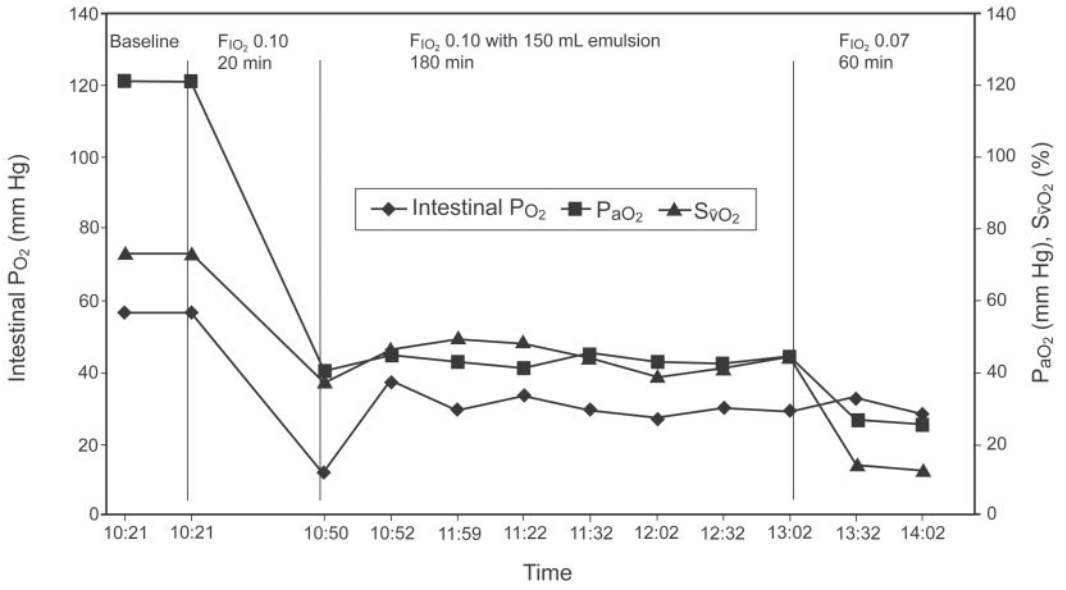

Fig. 5. Intestinal P_{O_2}, P_{aO_2}, and mixed venous hemoglobin oxygen saturation ($S_{\bar{v}O_2}$) profiles during hypoxic-hypoxia produced with F_{IO_2} 0.1 and 0.07 and instillation of 150 mL of the mesoporous silica H_2O_2 emulsion.

may be possible to create oxygen reserves (as there would be less systemic oxygen utilization by the splanchnic bed), which may become even more valuable in the setting where substantial lung injury concomitantly exists. Similar strategies using the topical application of oxygen to wounds and burns when edema and damaged vasculature impede traditional oxygen delivery to the tissues may be of value.[6,7]

Intravenous Chemical Oxygenation Revisited

As discussed earlier, intravenous and intra-arterial H_2O_2 have been given to humans with some measure of success. However, the lack of its widespread reported use over the last 40 years, indicates that safety is a major factor. Again, major challenges facing the use of intravascular H_2O_2 include the rate at which oxygen is produced in relation to how quickly it can be kept in solution in plasma. Rates of reaction are thus key. If this could be controlled, intravascular H_2O_2 use might have many major indications in medicine, including rescue therapy for the cannot-ventilate/cannot-oxygenate scenario in airway management, to cardiac arrest resuscitation where oxygen delivery to the heart and brain is flow limited and oxygen extraction at the level of the tissue is maximum. Its use as an adjunct in the treatment of stroke and myocardial infarction could even be entertained.

We have proposed and are working toward solutions to the challenges preventing safe usage of intravascular H_2O_2. We believe 2 major components that are essential to realizing this include slowing the rate of H_2O_2 release/availability for reaction with catalase, and providing a medium within the circulating plasma to allow additional dissolution of the oxygen that is created.

In regards to rate control, we are working toward various methods of H_2O_2 encapsulation that would provide for controlled release of H_2O_2 over time, so as not to overwhelm the ability of catalase to convert H_2O_2 to oxygen and water, as well as to keep oxygen levels from exceeding plasma solubility. This strategy requires high-level knowledge of water transport across biomaterials, which must be coupled with knowledge of blood flow and tissue oxygen consumption. Figure 6 demonstrates one such strategy. This approach attempts to microencapsulate the solid urea-H_2O_2 adduct in a biocompatible and water permeable coating of poly(lactic-co-glycolic acid) (PLGA). While the urea-H_2O_2 is split by water, this would be impeded by loading the capsule with a hydrophobic material such as a perfluorocarbon. The advantage of microencapsulation and controlled release is that H_2O_2 would be released and converted to oxygen throughout the circulation. This is opposed to direct delivery of H_2O_2 intravenously or intra-arterially, which basically would immediately react within seconds.

In regard to further optimizing H_2O_2 produced oxygen dissolution into plasma, concomitant use of compounds such as intravenous perfluorocarbons should enhance the solubility of oxygen in plasma, given their ability to carry nonpolar gases in substantially greater concentrations (over 5 volume percentage of oxygen) than plasma.[67]

The combination of these techniques, while complex, shows some promise in closed circuit experimental chambers. Since encapsulation coating thicknesses as well as

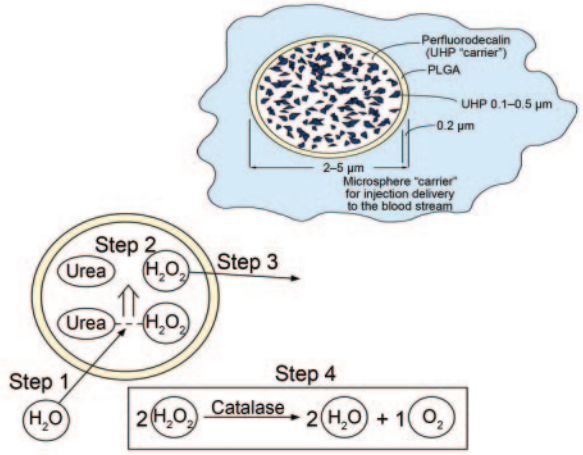

Fig. 6. Current working strategy of producing intravenous H_2O_2 delivery platform for intravenous oxygen production. Urea-hydrogen peroxide (UHP) and a hydrophobic carrier such as perfluorodecalin are encapsulated in a water permeable biocompatible coating such as poly(lactic-co-glycolic acid) (PLGA). The combination controls water entry into the microcapsule, allowing spitting of the urea-hydrogen peroxide (UHP) adduct into urea and H_2O_2, where H_2O_2 then leaves the capsule, making contact with catalase, where it is broken down into water and oxygen.

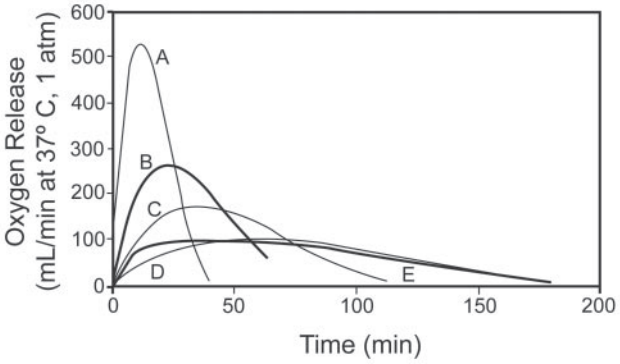

Fig. 7. Changing the loading of urea-hydrogen peroxide particles, size of microsphere, and thickness of capsule coating in Figure 6 will result in various release profiles of H_2O_2 from the microcapsule and thus oxygen production profiles.

the UHP loading of the microcapsules can be varied, different delivery profiles are theoretically possible that may allow for a single bolus of H_2O_2 to provide for prolonged oxygen production capable of matching some portion of oxygen consumption (Fig. 7). This controlled delivery and release of H_2O_2 with such a vehicle could theoretically create oxygen at a rate commensurate with consumption. Its creation throughout the vasculature would ensure that hemoglobin is continually saturated, with excess oxygen being dissolved in a circulating perfluorocarbon. It is particularly exciting to consider its production at the microcirculatory level, including capillaries and venules, which would help ensure that tissues are oxygenated despite areas that may be experiencing critical reductions in microvascular flow. Substantial additional engineering and biomaterials work is required before this strategy can be tested. Concerns, of course, will exist regarding the downstream potential free radical effects and tissue injury with such a strategy.[12,68] Concomitant use of antioxidants could mitigate such damage. The choice to use an oxygenation rescue that incorporates H_2O_2, may depend on the urgency of the clinical situation.

Summary

On-site chemically produced oxygen for human utilization is not new and has been experimented with for close to a century. However, its safe and ubiquitous use in healthcare is not yet realized. We have reviewed its use for breathable oxygen as well as its delivery as an intravascular and gastrointestinal agent to treat systemic and regional hypoxemia. A unique knowledge of chemistry, engineering, and physiology will be required to consider, optimize, and deal with the various challenges that could make chemically produced oxygen a valuable asset in emergency care.

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Discussion

Hess:* I'm sitting here thinking about a patient in the ICU with ARDS, and I can envision an intravenous cocktail of peroxide and THAM [trishydroxymethyl-aminomethane] that might be an alternative to ECMO [extracorporeal membrane oxygenation].

Kevin Ward: Yes. Now, how long you could make it run, I'm not sure, but peroxides have been looked at to use in membrane oxygenation when there's not gas around to do bypass. It's old literature, but THAM to consume CO_2 should be practical. I'd love to see that happen.

Jeff Ward: John Heffner's historical report noted that the early pioneers in oxygen manufactured O_2 by electrolysis.[1] Does that have any future?

Kevin Ward: Not until there's a huge leap in cathode technology. The thing is the fouling of the anode and cathode, and that's something the electrochemists have not been able to solve. The system has to be so pure. However, the amount of O_2 that can be released with the catalysis of water is huge. That would be the ultimate answer for storing O_2. But the electrochemistry challenges for that are extraordinary.

Branson: Kevin, because the dry chemistry basically lasts forever, have you looked at larger systems that you could drive in after a disaster and set up and start creating oxygen?

Kevin Ward: We would love to see that happen, but you'll never reach the efficiency of the concentrator if you have electricity or liquid O_2 systems if there is no supply problem. There's always some price to pay for the dry chemistry. To make the dry chemistry safe you'd have to probably use the percarbonates. Candle chemistry is not the answer. The candle chemistry is attractive because it's the most efficient solid, in terms of making the most O_2 per weight. The problem is how it's made with that temperature.

If you had a big block the size of this room, you could make a heck of a lot of O_2. The issue would be insulating it and making sure you don't melt down to the middle of the earth. Its attractive that the stuff doesn't break down and you can keep it for a really long time, but controlling the rate of reaction, coupled with the fact that you can't turn it on and off, is problematic. Once you start these solid peroxides into action, that's a problem. That's why I like the idea of converting usable solids into a liquid that then can be metered into a system as needed.

Branson: We've tested some of these things for the military special ops community. There's one about twice the size of a soda can, and when you do thermal imaging, it's at 350°F. Sometimes they take them not to deliver O_2 but just to warm up their hands.

Kevin Ward: One of them was advertised to help mitigate heat loss during shock. The FDA says the outside temperature of these things has to be less than 45°C, but none are FDA approved, certainly not for over-the-counter use. And storage is an issue. As you look at the indications for these devices that create 6 L/min of O_2 for

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15 minutes, you have to ask yourself, in what scenario is this useful? This would be especially true for any military application.

Branson: I think it's important that, for some reason, the O_2 in airplanes is considered emergency O_2 and is not governed by the FDA. And some people have made these devices thinking they aren't governed by the FDA either, and I think those people have made the wrong assumption.

Kallet: In a disaster scenario, particularly in a cold weather situation where you don't have electricity, could the heat have a useful purpose outside of O_2 delivery?

Kevin Ward: Sure. There's a whole science of heat transfer. You could use the heat to boil water to make steam and run something. The issue would be getting the investment for somebody to create that sort of infrastructure to make it happen. The cost and lead times may be a bit perilous. Certainly, if you're going to create a system like that to use, you'd want to leverage every bit of the chemistry you can for the common good. Having an area of the device to heat your water or cook on, that sort of stuff, would be good, but 500–800°C is a lot of heat to deal with safely.

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