ENHANCED SOLUBILITY WATER

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Introduction

Enhanced Solubility Water (ESW) is purified drinking water which has been altered by a highly advanced and proprietary process to be more soluble to gas. ESW technology is based upon the hypothesis that the structure of water can be altered so that it is more soluble to non-polar gases, in particular, oxygen. It appears that this property makes ESW beneficial to humans. As Professor Martin Chaplin, Head of Food Research Centre, London South Bank University, has stated "Liquid water (H_2O) is often perceived to be pretty ordinary as it is transparent, odorless, tasteless, and found everywhere. However, it is the most remarkable substance…Water seems, at first sight, to be a very simple molecule, consisting of just two hydrogen atoms attached to an oxygen atom. Indeed, there are few molecules that are smaller or lighter…The size of the water molecule, however, belies the complexity of its actions and its unique capabilities and anomalous properties seem to fit ideally into the requirements for life as no other molecule can."[1]

Gas Solubility, Water Cavities, and Clathrates

Chaplin's compilation of scientific observations describes the complex structures of water and elucidates its mysteries. Specifically, these observations, together with the non-classical nucleation theory of solubility, describe the spontaneous occurrence of transient, tiny cavities in water which can be occupied by single guest molecules like oxygen (O_2) or other non-polar gases. It is believed that when oxygen becomes dissolved, a single molecule enters a cavity and stabilizes it. The shell of the cavity is composed of a layer of about 25 water (H_2O) molecules that resembles a cage-like structure (i.e., a clathrate) as shown below.

Figure 1. Examples of small clathrates composed of water molecules.

sI sII

Tetrakaidecahedral ($5^{12}6^2$) and hexakaidecahedral ($5^{12}6^4$) cavities found in crystalline gas clathrate structures sI and sII respectively.

The solubility for oxygen in water is very low and is governed by Henry's Law which predicts the amount of dissolved oxygen in relation to temperature and partial pressure of oxygen at the gas/water interface. At equilibrium, under ambient conditions, the amount of dissolved oxygen in one liter of H_2O is about 8mg (6 ml O_2). The dissolved oxygen resides in water as single molecules occupying tiny water cavities. If more oxygen is forced into the water, by increasing the partial pressure of the gas, thus exceeding the saturation point, the additional oxygen resides as invisible micro-bubbles or nano-bubbles and is not truly dissolved as simple molecules. In this situation, when the pressure is released or the water is agitated, the excess oxygen gas escapes as bubbles. This is similar to the behavior of a carbonated beverage. Within minutes, the amount of retained oxygen returns to its original value of about 8 mg per liter.

Larger Cavities Containing Oxygen Clusters in ESW

ESW is purified water containing 3 to 4 times the amount of dissolved oxygen when compared to untreated water (oxygen values for ESW are 22 to 30mg per liter H_2O). No bubbles are formed with agitation and the elevated oxygen levels remain for one day or longer after exposure to the atmosphere, indicating that the additional oxygen is actually dissolved and is not in bubble form. According to Dr. Bertrand Guillot, Director of Theoretical Liquid Physics, University of Paris, it is likely that the Otec proprietary process results in larger water cavities occupied by clusters of two or more oxygen molecules. He believes these larger cavities have larger shells resembling clathrate structures composed of more than 35 H_2O molecules. The persistence of elevated oxygen levels in ESW despite agitation suggests that the larger water cavities are also stabilized by the oxygen clusters.

The proprietary process which generates ESW likely increases the solubility of purified water for oxygen by creating oxygen clusters retained in larger water cavities. This novel composition persists for months in closed bottles and for a day or more in open containers. It is believed that upon consumption, ESW's larger water cavities improve tissue oxygenation.

Oxygen Transport Physiology and Human Effects of ESW

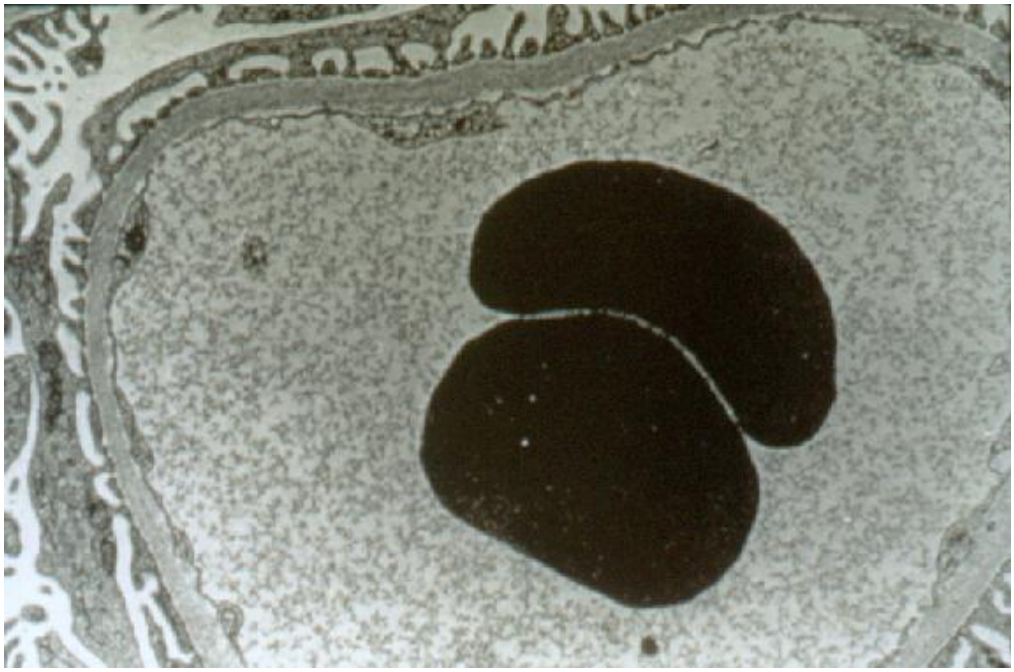
In controlled, blinded, and randomized studies, elite cyclists were shown to perform with lower heart rates at fixed workloads and had increased speed at predetermined heart rates after consuming ESW. In addition, in similarly designed studies, patients with claudication due to lower extremity peripheral vascular arterial disease and patients with chronic stable angina were shown to walk further, and to recover faster after drinking ESW.

The mechanism by which ESW produces these physiologic effects is unique, since the concentration of oxygen alone, in a liter of ESW, is not sufficient. Under resting conditions, the average adult inspires and delivers to the body, about 250 ml of oxygen per minute via the bloodstream. Despite the 300% increase in O_2 content in ESW compared to tap water, the amount of O_2 contained in a liter of ESW represents only 10 percent of the O_2 utilized per minute. An alternative explanation for the observed improvement in performance in athletes and in patients is that ESW improves oxygen diffusion in the circulatory system.

Oxygen Transport: Convection and Diffusion

In the human circulatory system, under ambient conditions, approximately 98% of the oxygen is carried (convected) by hemoglobin in the red blood cells (RBC) and 2% is found in the plasma. Since the average adult normally inspires and delivers about 250 ml of O_2 per minute, only 5 ml of O_2 is actually delivered to tissues via the plasma phase of blood. When RBC enter the microcirculation, specifically the capillaries, the release of oxygen from the RBC is normally retarded by the low solubility of oxygen in plasma since plasma is mainly composed of water. It is estimated that up to 75% of the resistance to oxygen diffusion from the RBC is due to the low solubility of oxygen in plasma. Because RBCs are only in the capillaries for a fraction of a second, the diffusion rate of O_2 from the RBC is a critical factor in determining how much oxygen becomes available to the tissues. Thus the quantity of oxygen made available to tissue cells not only depends upon the amount of O_2 convected by the RBC (and to a much lesser extent, the plasma), but also on the diffusion rate of O_2 from the red blood cells. It is believed that when ESW is present in the plasma, it increases the diffusion rate of oxygen from the RBC by temporarily increasing oxygen solubility in plasma. This effect is estimated to last for several hours.

Figure 2. Capillary Cross Section

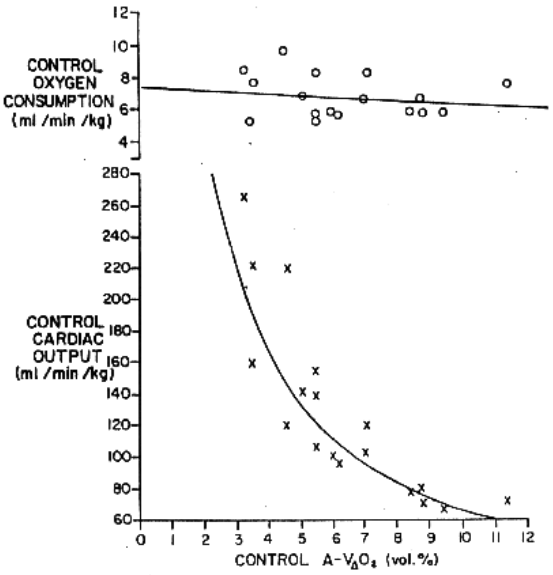


Schematic: Similar to molecular hemoglobin in plasma, ESW increases O_2 diffusion from red cell to vessel wall.

Heart Rate Is Inversely Related to Oxygen Diffusion

Increasing oxygen diffusion by ESW and thus lowering heart rate, may, by analogy, be similar to the observed behavior of free hemoglobin molecules in plasma and is in agreement with basic oxygen transport physiology. Changes in cardiac output (reflected in heart rate) are inversely related to global oxygen extraction (diffusion). This reciprocal relationship, described in 1973 by A.C. Guyton, et al., infers that increases in oxygen extraction (diffusion) are automatically offset by decreases in cardiac output (and heart rate) (Figure 3).[2] Importantly, the relationship functions to ensure that the correct amount of oxygen is available for tissue consumption without resulting in hyperoxia (too much oxygen being made available to tissues). At sub-maximal exercise effort, the auto-regulatory effect of increasing oxygen diffusion is to satisfy the demand for oxygen at a lower heart rate.

Figure 3. These experimental data indicate that oxygen consumption is maintained by the reciprocal relationship between cardiac output and oxygen extraction, inferring that decreases in heart rate are associated with increases in diffusive oxygen transport.



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Further support for this hypothesis can be inferred from *in vitro* and *in vivo* studies.[3] *In vitro* experiments utilizing an artificial capillary established that the diffusion rate of oxygen from RBC could be significantly increased by adding low doses of molecular hemoglobin to plasma (Figure 2).[4] These studies suggest that the rate of oxygen diffusion from red cells is influenced by the capacity of the plasma to receive oxygen. When molecular hemoglobin is added to plasma, additional O_2 receptor sites become available, not only increasing plasma oxygen content but also facilitating oxygen release to tissues. By analogy, it is believed that when ESW, with its larger oxygen cavities, is absorbed from the gastrointestinal tract into the bloodstream, there is a transient increase in plasma oxygen solubility and concomitant enhancement of oxygen diffusion.

Similar effects were seen in *in vivo* studies which demonstrated that the intravenous administration of a low dose of molecular hemoglobin to cyclists allowed them to maintain sub-maximal work output at reduced heart rates.[5] The effect was attributed to an increase in oxygen diffusion in the plasma since the dose of molecular-hemoglobin administered was too low to account for the decrease in pulse rate. Lower heart rates were also seen in subjects after consumption of ESW, suggesting a relationship with increased plasma oxygen diffusion.

Exercise Effects of ESW

Initial randomized and blinded studies assessed the physiologic effects of ESW on athletes. Elite cyclists were chosen for these studies to minimize variability in test conditions. Cyclists used their own bicycles on stationary rollers with computer controlled resistances and simulated distances. Heart rates were recorded from pulse monitors. Because of their advanced training these athletes were able to maintain specified heart rates for sustained periods of time.

Study ESW – 001: Single Blind, Randomized, Two-Way Crossover, Tap Water Controlled, Sub-Maximal Exercise Test to Determine the Effect of Enhanced Solubility Water (ESW) on Heart Rate

Study site: NorCal Bicycle Testing Facility, Santa Rosa, CA

The results demonstrated no significant change in pulse rate comparing baseline to test results when the cyclists drank TW. In contrast, after drinking ESW, there was a statistically significant decrease in heart rate for each resistance level tested, (p value = 0.01 for 80% Lactate Threshold (LT) p = 0.012 for LT + 20 watts, p = 0.0053 for LT + 40 watts, and p = 0.0203 for LT + 60 watts).

This study suggested that consumption of ESW enhanced tissue oxygenation as the cyclists were able to perform the same work with lower pulse rates.

Study ESW – 002: Single-Blind, Randomized, Tap Water Controlled, Sub-Maximal Exercise Test at a Predetermined Heart Rate to Ascertain the Effect of Enhanced Solubility Water (ESW) on Cycling Speed Over a Five-Mile Simulated Distance

Study site: NorCal Bicycle Testing Facility, Santa Rosa, CA

The results showed that after consuming ESW, the cyclists, while maintaining their pulse rates constant, were statistically significantly faster for miles 2-5 and for the full five mile course ($P < 0.05$), than after ingesting TW.

Since Studies ESW – 001 and ESW – 002 demonstrated markedly positive physiologic effects of ESW, a larger more definitive study was performed.

Study ESW - 003: Double-Blind, Randomized, Tap Water (TW) Controlled, Sub-Maximal Exercise Test at a Predetermined Heart Rate to Ascertain the Effect of Enhanced Solubility Water (ESW) on Cycling Speed Over a Ten-Mile Simulated Distance

Study site: NorCal Bicycle Testing Facility, Santa Rosa, CA

In this study, the physiologic effect of drinking ESW was demonstrated in cyclists who were able to complete a ten mile simulated distance in less time, while maintaining a fixed heart rate than when the cyclists drank TW. This study confirmed the results of Study ESW - 002 which showed similar results when cyclists completed a five mile simulated distance at fixed heart rates and Study ESW-001 in which the physiological effect of drinking ESW by the athletes was shown to be a lowered heart rate while accomplishing the same work output. These tests were performed by elite athletes in whom oxygen is used efficiently. It is likely that ESW may also prove beneficial to individuals whose use of oxygen is less efficient, such as in patients who experience intermittent claudication (IC) due to peripheral arterial obstructive disease (PAOD) or in patients with chronic stable angina.

Effects of ESW on Intermittent Claudication

Rationale for Studying Intermittent Claudication

ESW appears to help the body oxygenate itself better. ESW was initially tested on elite cyclists who arguably use oxygen more efficiently than any other population and, therefore, would be expected to respond less dramatically. Since the results of these studies were markedly positive, ESW was tested in a group of subjects with lower limb claudication as produced by peripheral arterial obstructive disease (PAOD), a disease process

which produces symptoms specifically due to poor oxygenation. In particular, the study was limited to femoral-popliteal disease causing calf claudication.

"Intermittent claudication is a clinical condition of muscle pain in the lower extremity induced by exercise and relieved by short periods of rest. It is caused by fixed arterial obstruction at sites proximal to the affected muscle bed such that the normal exercise-induced increase in muscle blood flow cannot occur to a degree sufficient to meet the metabolic demands of the exercising muscle."[6] (p. 930).

There are three essential features. "The pain is: (1) always experienced in a junctional muscle unit, (2) reproducibly precipitated by a consistent amount of exercise, and (3) promptly relieved by mere stopping of the exercise"[7] (p. 920) The "fixed arterial obstruction" is generally caused by arteriosclerosis of the involved vessel.

Patients with IC were chosen as test subjects because the disease is common, easy to diagnose, reasonably safe to test and the symptom debilitating enough to be worthy of concern. Additionally, current pharmacological treatment of IC is not optimal and may even be considered clinically ineffective. The pain of claudication is brought on by inadequate tissue oxygenation and is elicited by a consistent and reproducible amount of exercise. The beneficial tissue oxygenating effects of ESW may enable IC patients to exercise for longer periods of time before experiencing symptoms.

Intermittent claudication, the most common debilitating symptom of PAOD, is a very common condition; it is estimated that 12 to 17% of the population aged 50 to 70 is affected by PAOD[8] (p. 929). "In 1987 an estimated 4,234,000 people in the United States had IC."[9] It is obvious from this estimate that there is a wealth of patients available for testing and treatment.

Diagnostic methods confirming the presence of PAOD are effective, safe, and non-invasive. In most circumstances the ankle-brachial systolic pressure index (ABI), a simple non-invasive test, "clearly identifies the patient with claudication and allows quantification of the severity of the symptoms."[10] (p. 931) If necessary, the ABI can be performed pre- and post-exercise. Pulse volume recording, segmental pressure measurements, and duplex scanning are also readily available and safe if additional testing is required for confirmation of IC.

Claudication is an unquestionably debilitating, lifestyle-limiting symptom. Regensteiner et al found that patients with IC are severely impaired in their ability to perform their daily activities.[11] This impairment was confirmed by lower quality of life scores on both physical and disease specific scales.[12]

Perhaps of most importance, claudication is a relatively safe condition to test since it is not life-threatening. In fact, it rarely progresses to severe ischemia with the need for amputation. With 10-year follow-up, amputation rates have ranged from 0 to 12%. Symptoms have remained stable or improved in about 80% of patients.[13] (p. 931) Although PAOD is often accompanied by cerebrovascular disease (52%) and coronary arteriosclerosis (90%), these risk factors can be excluded by a thorough history and physical exam.[14]

Finally, there is an obvious need for an effective pharmacologic treatment for IC. Coffman summarized the results of trials designed to evaluate various classes of agents for PAOD. "Drug therapy for patients with intermittent claudication has not been successful."[15] (p. 264) In particular he looked at Pentoxifylline which is the dominant drug prescribed for IC in the United States. He stated, "Our initial clinical experience with Pentoxifylline in patients with mild to moderately severe intermittent claudication agrees with the second study showing no benefit."[16] (p. 261) Pentoxifylline has the usual array of side effects with one study showing nausea at 28.8% with the capsule form.

Since IC either stabilizes or improves in 80% of patients, the more aggressive approaches like surgery or percutaneous angioplasty are reserved for cases which fail to respond to conservative treatment. Thus, IC is an ideal symptom complex to study. The pain is directly related to inadequate oxygenation – a state which ESW may improve.

ESW - 004: Single-Blind, Randomized, Tap Water Controlled, Treadmill Exercise Test to Determine the Effects of Drinking Enhanced Solubility Water (ESW) on the Onset and Duration of Claudication in Patients with Known Lower Extremity Peripheral Arterial Obstructive Disease (PAOD)

Study Site: Russian Academy of Science – Institute of Medical Biological Problems, Moscow

With Tap water (TW) neither time to the maximal pain nor the recovery from pain had a statistically significant change with respect to baseline. However, the changes in both parameters were significant with ESW. With regard to maximal pain, the mean improvement was 10.4% ($p < 0.05$). With ESW there was a 30.1 % reduction in the mean duration of pain per subject with a very high statistical significance ($P< 0.001$).

Based on these encouraging results, a larger double-blinded crossover study was performed.

ESW – 005: Double-Blind, Randomized, Tap Water (TW) Controlled, Treadmill Exercise Test to Determine the Effects of Drinking Enhanced Solubility Water (ESW) on the Onset and Duration of Claudication in Patients with Known Lower Extremity Peripheral Arterial Obstructive Disease (PAOD)

Study Site: Russian Academy of Science – Institute of Medical Biological Problems, Moscow

After drinking ESW, the time which subjects were able to walk before the occurrence of maximal pain was increased 23% on average per person. This was very highly significant ($P<0.001$). With TW, there was no statistical improvement in this parameter. Again, with ESW, the recovery time from maximal pain was reduced by 16% average per person ($P= 0.001$). TW had a 10% average reduction per person ($P= 0.014$), indicating a hydration effect.

The encouraging results of this test were confirmed and exceeded in a second study (ESW – 006) in which the patients were hospitalized to minimize the impact of variables (smoking and drinking of alcohol) and to obtain consistent consumption of water. Furthermore, to reduce variation in the treadmill procedure, it was simplified by using a single speed and incline for all patients.

ESW – 006: Pilot Double-Blind, Randomized, Tap Water Controlled, Crossover Study to Determine the Effects of Enhanced Solubility Water (ESW) in Patients with Symptomatic Lower Extremity Peripheral Vascular Obstructive Disease (PAOD) and Intermittent Claudication (IC)

Study Site: Central Clinical Hospital of the Russian Academy of Sciences, Moscow

For time to maximum pain, there was a difference between the ESW treatment and the TW treatment groups in the change from baseline with a median value of 35 seconds, a mean of 80 seconds, and p-value of .0002 by Wilcoxon test. There was no significant change in time to maximum pain from baseline in the TW group, but

the ESW group had an increase from baseline of 43 seconds (median) or 89 seconds (mean) that differed from 0 with p = .0001.

For Time to Pain Relief, there was a difference between the two arms in the change from baseline that had mean value of -152 seconds and median of -91.5 seconds. The difference was significant at the .009 level using a Wilcoxon test. For the ESW group, the mean and median change were -117 seconds and -.90 seconds respectively, and there was a significant decrease from baseline (p = .02). For the tap water group, the mean and median change were 35 seconds and 20 seconds respectively, and there was a significant increase from baseline (p = .009).

This pilot clinical trial confirms the results of previous studies in patients with claudication. In all three, in contrast to data obtained after consuming TW, patients that ingested ESW demonstrated substantial and consistent improvements over baseline values with respect to walking times and recovery times. These studies suggest that the consumption of ESW results in a predictable lengthening of the exercise time and shortening of the recovery time of individuals with intermittent claudication.

In the current study, testing variability was decreased by hospitalizing the patients and simplifying the treadmill procedure by using a single speed and incline for all patients, likely leading to the more pronounced differences that were seen in exercise and recovery time in the two treatment groups.

ESW – 007: Pilot Double-Blind, Randomized, Tap Water Controlled, Crossover Study to Determine the Effects of Enhanced Solubility Water (ESW) in Patients with Chronic Stable Angina (CSA)

Study Site: Central Clinical Hospital of the Russian Academy of Sciences, Moscow

For time to maximum pain, the difference between the ESW treatment arm and the TW treatment arm in the change from baseline had a median value of 40 seconds, a mean of 58 seconds, and p-value of .011 by Wilcoxon test. There was no significant change from baseline in the TW group, but the ESW group had an increase from baseline of 60 seconds (median) or 62 seconds (mean) that differed from 0 with p = .004.

For the time to pain relief, there was a difference between the two arms in the change from baseline that had a mean (-131 seconds) and median (-30 seconds). The difference was significant at the .003 level using a Wilcoxon test. For the ESW group, the mean and median change were both -20 seconds, and there was a significant decrease from baseline (p = .02). For the TW group, the mean and median changes were 11 seconds and 0 seconds respectively and there was no significant change from baseline.

In contrast to patients who ingested TW, patients who consumed ESW were able to exercise for longer periods of time on the treadmill. When pain was experienced they were also able to recover in less time. These data demonstrate that drinking ESW has a beneficial effect on both the onset and duration of chest pain in patients with Chronic Stable Angina, and suggest that ESW could benefit patients with other medical conditions characterized by suboptimal tissue oxygenation.

Discussion

The results of seven blinded randomized human studies indicate that the consumption of ESW improves exercise performance in athletes and ameliorates, during exercise, the occurrence of claudication in patients with peripheral vascular disease and chest pain in patients with chronic stable angina. The crossover design of these investigations was intended to minimize the day-to-day variations in performance which are subject to the influence of many factors including diet, random hydration, smoking, exercise and sleep patterns. These

positive results are not likely due to the increased oxygen content of ESW. Although the mechanism of action is unknown, it is postulated that ESW has greater solubility for oxygen due to larger water cavities and that this property is transiently conveyed to the plasma when ESW is consumed and absorbed from the gastrointestinal tract. It is believed that the phenomena of reduced heart rates and the increased speed observed in athletes are due to enhanced oxygen diffusion. Similarly, the positive effects with regard to claudication and chronic stable angina are also thought to be due to improved oxygen diffusion in the presence of restricted blood flow.

Summary

It was postulated that ESW, because of its property of increased O_2 solubility, would act in the plasma to increase O_2 diffusion to the tissues. This effect was manifested in elite athletes as a decrease in heart rate at fixed workloads and increased speed at predetermined heart rates. In claudication and chronic angina studies, the effect was further demonstrated as a lengthening of the time to maximal pain and a shortening of recovery from this pain.

While the results of these studies are not conclusive, they strongly suggest that ESW has a potential benefit in health and in certain disease states. Additional studies are planned.

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