Ultra-Fine Oxygenated Nanobubbles for the Post-COVID19 Syndrome Patient

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Background

In late 2019, the SARS-CoV2 virus began to spread across the globe causing a global pandemic and the emerging infectious disease COVID-19. With millions of confirmed cases and over 3 million deaths, a percentage of individuals with COVID-19 develop severe acute respiratory syndrome, severe hypoxia, systemic hypercoagulation, and chronic lung dysfunction. One of the hallmarks of COVID-19 is the long-term sequela that persists after recovery of the acute syndrome. Long-COVID includes persisting symptoms such as fatigue, impaired pulmonary function, chronic hypoxia, dyspnea, muscle weakness, and decreased return to normal activity. We hypothesize the use of the Bimini Ultra-Fine Bubble (UFB) hydrotherapy, a nanobubble oxygenation technology, will aid the recovering patient by increasing oxygenation of peripheral tissues, increasing systemic oxygenation, therefore improving fatigue, muscle weakness and allowing for improved return to activity. We aim to combine this therapy with near-infrared spectroscopy (NIRS), using products from Moxy and Nonin, to measure regional oxygen saturation and muscle oxygen saturation.

The Bimini UFB hydrotherapy system continuously infuses water with ultra-fine air bubbles that are less than 0.1 microns in size. On average, human skin pores are 50 microns in size which nanobubbles should penetrate with ease. This has the potential to supply additional oxygen to peripheral tissues. One proposed mechanism is that effective oxygen delivery may increase reactive oxygen species at therapeutic levels to initiate an early cascade of valuable growth factors and neovascularization. Additionally, it is proposed that an increase in oxygen allows for vasoconstriction, decreased vessel permeability and decreased edema, therefore diminishing diffusion distance for optimum oxygen delivery (5).

One area that is now being researched is hyperbaric oxygen therapy (HBOT) for COVID19 patients. An understanding of HBOT is crucial in predicting the vast potential for UFB, as both therapies provide hyperoxygenated environments for peripheral tissues. Initial research points toward HBOT effectively delivering oxygen to patients with ventilation perfusion mismatch, bronchoalveolar hypoperfusion, and bilateral pneumonias. COVID-19 is partially due to an overly active immune response generating systemic inflammation, HBOT has been shown to reduce inflammatory reactions. A study published in 2019 by Chen et al. showed a decreased serum concentration of intracellular enzymes as a surrogate for muscle damage and decreased pain and fatigue in athletes with muscle injuries when treated with multiple sessions of HBOT compared to the control group (1). These examples are just a glimpse of the benefits that increased oxygen environments may have in recovery.

NIRS is a non-invasive technology that utilizes multiple lasers and detectors to determine mixed venous blood oxygen saturation of tissues 1-3 cm below the sensors by measuring the absorption spectra of the tissue chromophores oxyhemoglobin and deoxyhemoglobin. The mixed venous oxygen saturation is affected by many aspects of physiology, but overall represents the relationship of oxygen delivery and utilization in tissues (3, 4). To showcase the utility of this non-invasive technology, one study performed by Marimón et al. compared NIRS placed over the cerebrum to oxygen saturation from mixed venous samples taken from central venous catheters in pediatric patients undergoing heart surgery and found a moderate and significant correlation (4). Therefore, NIRS can be trusted as a non-invasive measuring tool to acquire mixed venous oxygen concentration in our study. One NIRS sensor in our study is the Moxy device that we will utilize to record muscle oxygen saturation (SMO2) of the rectus femoris muscle. The other is the Nonin device that we will utilize to record regional oxygen saturation (rSO2) over the femoral vessels.

Using the same experimental protocol, we found both the rSO2 and SMO2 to increase in healthy athletes. SMO2 increased 86% on average and rSO2 increased 4.5% during an unpublished preliminary trial. Eight individuals were tested using the BIMINI to provide hyperoxygenation to bilateral lower extremities. After 35 minutes exposure to 17-18 parts per million (ppm) hyperoxygenated water, subjects saw their SMO2 peak at 87% on average (Figure 1). From time zero to 35 minutes, oxygenation increased by 86%, with a Chi-square of 46.07, change from time zero was statistically significant at <0.0001 and treatment between time points had a fixed effect of 0.0006 P value (Mixed-effects Analysis Model Type III) (Figure 2). Due to missing data points and variable time frames for each experiment, a mixed-effect analysis model was preferred over analysis of variance testing (ANOVA). Individual paired t-tests of time zero to each timepoint found statistical significance at each phase. Even after just 5 minutes, the difference was statistically significant with an average increase of 38.7% (p-value: 0.0242, paired t-test) (Figure 2).

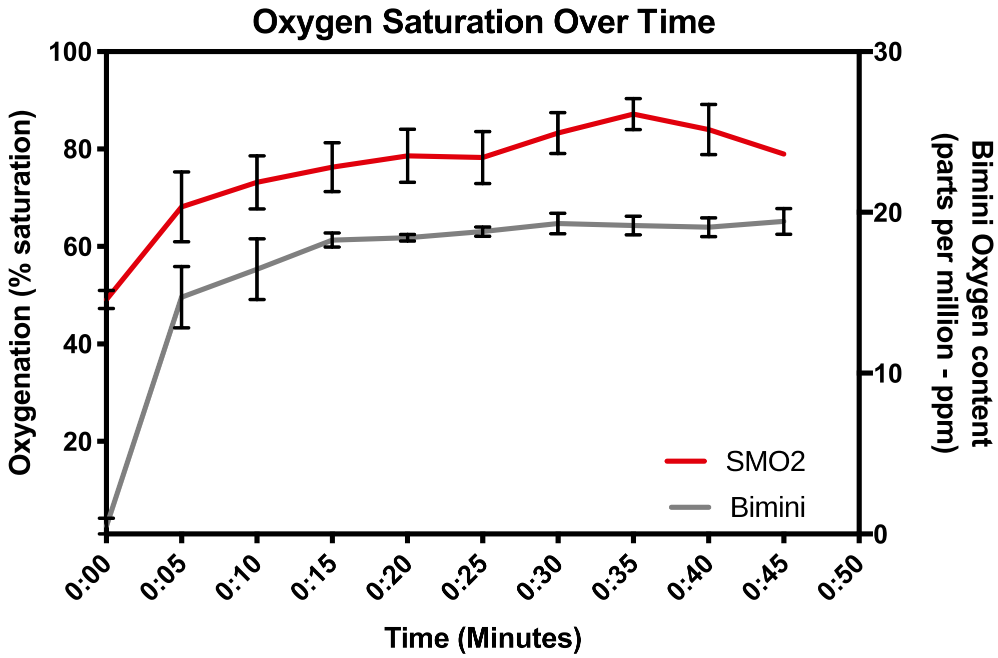

Figure 1. *Real time oxygenation values of the right rectus femoris utilizing an SMO2 sensor. Real time oxygenation values of the bath water used for treatment during the time of Bimini UFB infusion. N=8.*

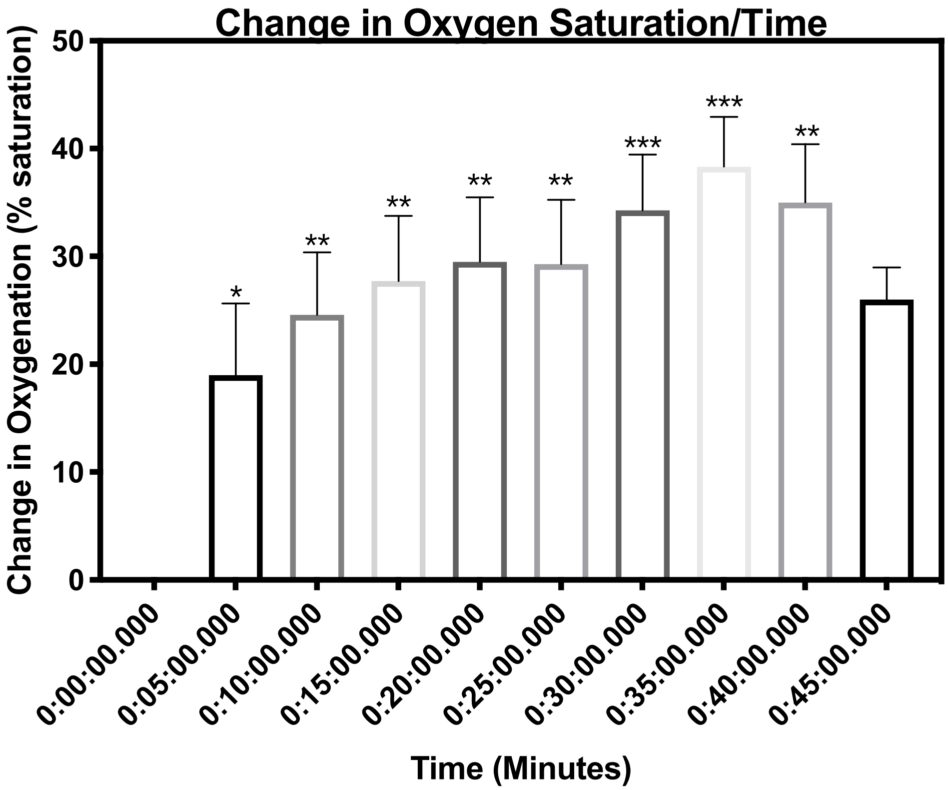

Figure 2: *Change in oxygenation of the right rectus femoris utilizing an SMO2 sensor from time zero. N=8. Statistical significant asterisk represent comparisons of each time point with time zero. * = p-value < 0.05; ** = p-value < 0.01; *** = p-value < 0.001.*

Subjectively, patients undergoing long-covid experience fatigue and a decrease in the ability to perform everyday tasks. To assess subject's qualitative improvement, the Lower Extremity Functional Scale (LEFS) and the Western Ontario and McMaster Universities Arthritis Index (WOMAC) both assess activities of daily living, functional mobility, gait, general health, and quality of life. The WOMAC index, originally designed for patients with osteoarthritis, assess pain, stiffness, and physical functioning of the hips and knees assessing activities of daily living. From 0 to 96, higher WOMAC scores indicate worse pain, stiffness and functional limitations. The LEFS scale assess one's ability to perform everyday tasks and was specifically designed to monitor patients over time and to evaluate the effectiveness of an intervention. Lower scores indicate greater disability, with a max dysfunctional score of 80. In this study, we tested subjects before their treatment, 6 hours after treatment and 24 hours after treatment.

The goal of this research is to reduce long-covid sequela, increase time to return to activity, and reduce fatigue and weakness of patients experience long-covid symptoms. In this paper, we present 5 cases demonstrating the validation and potential of the Bimini UFB infuser for the post-COVID-19 patient. Each case presents data of SMO2 and rSO2 readings during treatment. The potential benefit with this technology is extensive and this area of research is calling for further exploration.

Materials:

Bimini UFB Hydrotherapy System
Dynamic Temperature and Oxygenation Probe
Moxy Sensor of the Moxy Monitoring System
Nonin SenSmart Universal Oximetry Systems

Methods:

Each patient was consented and eager to participate in this study. Each was evaluated and cleared for participation prior to the study by a board-certified sports medicine and board-certified internal medicine physician and professional sports physiologist. They were continuously monitored during the study by both a board-certified sports medicine and board-certified internal medicine physician.

During the study, each participant wore a neoprene sleeve on the right thigh that held the Moxy SMO2 sensor in place over the right rectus femoris. A Nonin NIRS sensor was placed in the left groin over the femoral vessels and secured with water resistant adhesive. These sensors provided real time capture and continuous monitoring of SMO2 and rSO2.

Prior to entering the bathtub equipped with a Bimini UFB infuser, Bimini ran for 10 minutes reaching an oxygen content between 14 - 22 parts per million (ppm). Their initial SMO2 and rSO2 and the tubs oxygenation and temperature were recorded. Each minute of the study, data points were collected.

Each individual was positioned in a resting position with bilateral lower extremities and lower trunk submerged except for the very top of the Moxy and Nonin sensors which were kept above the surface for data capturing purposes. Treatment time was 30 minutes. Tub temperature maintained between 90 to 101 degrees Fahrenheit throughout the treatment protocol. After the 30-minute treatment, each participant was transferred out of the bath where they stood to dry off and recover. The study period was completed at this time.

Subjects completed both a WOMAC and LEFS questionnaire prior to treatment and also 6 hours and 24 hours after treatment.

Case 1: LS

Description:

LS is a middle-age female, diagnosed with covid in November of 2020. Prior to diagnosis she was a fully functioning athlete running marathons and exercising around 5 times a week. 4 months after diagnosis, she was still experiencing daily fatigue and was unable to walk upstairs without dyspnea on exertion and spikes in her heart rate up to 80% of her max heart rate.

On exam, LS is a healthy, middle age female. She has normal vitals at rest in addition to benign cardiac and pulmonary exams. She exhibits full range of motion in her extremities. LS has a history of Renaud's syndrome without active symptoms.

Results:

Due to data transmission errors with the rSO2 and SMO2 sensor, not all time points were collected. Initial baseline oxygenation was recorded at time 0:00. rSO2 rose from 39% to 55% throughout the treatment. SMO2, while baseline measured 28%, initially dropped to 24% then rose to 63%. The water oxygenation with Bimini progressively increased from 14.25 to 17.65 during the treatment. Water temperature dropped slowly from 96.7 to 95.2 degrees Fahrenheit.

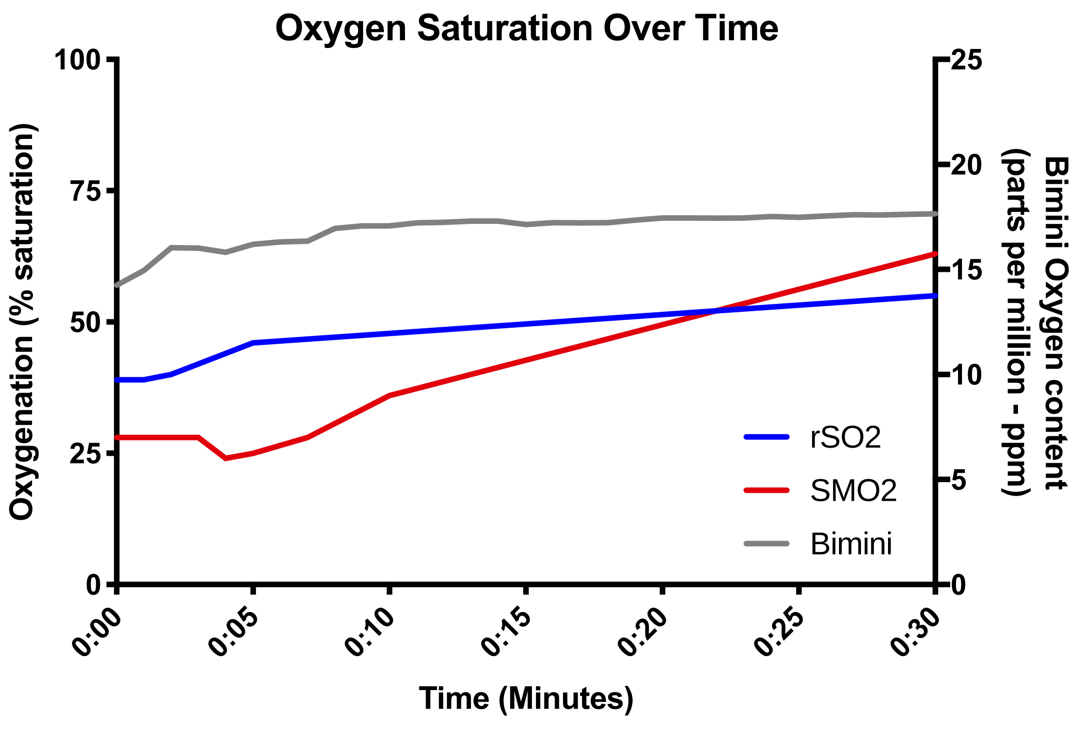

Figure 3. Real time oxygenation values of the right rectus femoris and the left femoral mixed venous sampling (rSO2) utilizing the Moxy and

Nonin sensors, respectively. Real time oxygenation values of the bath water used for treatment during the time of Bimini UFB infusion.

Subjectively, LS did not feel any change during the treatment. She experienced no side-effects. Following the Bimini treatment, she noted a slight improvement in her exercise ability but continued fatigue post-COVID.

Case #2: MT

Description:

MT is a middle-age female, diagnosed with covid in December of 2020. Prior to diagnosis she was a fully functioning active adult exercising 3-5 times a week. 3 months after diagnosis, she was still experiencing daily fatigue and was unable to return to exercise.

On exam, MT is a healthy, middle age female. She has normal vitals at rest in addition to benign cardiac and pulmonary exams. She exhibits full range of motion in her extremities. MT has a history of hypothyroidism.

Results:

All data points were collected for the rSO2 Nonin sensor, SMO2 Moxy sensor, Temperature, and oxygenation at 60 second intervals. Initial baseline oxygenation was recorded at time 0:00. rSO2 rose from 50% to 66% throughout the treatment. SMO2, baseline 23%, initially dropped to 20% then rose to 83% at 0:11 minutes, then remained consistent between 44-29. After removal of the Moxy Sensor, water was observed between the sensor and the right rectus femoris. Due to this water proofing issue, it is unable to assess the validity of the SMO2 results. The water oxygenation with Bimini progressively increased from 16.43 to 20.87 during the treatment. Water temperature dropped slowly from 93.7 to 92.2 degrees Fahrenheit.

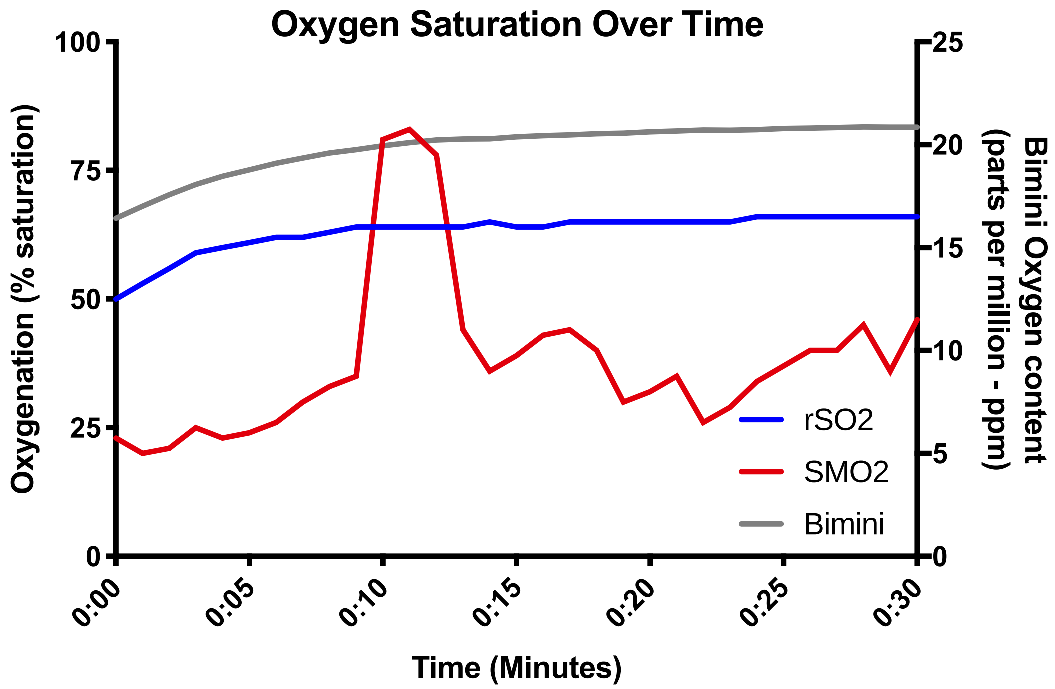

Figure 4. Real time oxygenation values of the right rectus femoris and the left femoral mixed venous sampling (rSO2) utilizing the Moxy and Nonin sensors, respectively. Real time oxygenation values of the bath water used for treatment during the time of Bimini UFB infusion.

Subjectively, MT did not feel any change during the treatment. She experienced no side-effects. After the treatment she did feel an improvement after 24 hours. Her WOMAC score, baseline 12, went down to a 2 at 6 hours and down to 1 at 24 hours showing an improvement in functioning. Her LEFS score, baseline 59, was 58 at 6 hours and increased to 64 at 24 hours showing an improvement in her daily functionality.

Case 3: AS

Description:

AS is a middle-age female, diagnosed with covid in July of 2020. Prior to diagnosis she was a fully functioning active athlete, competing in triathlons, exercising 5 times a week. 7 months after diagnosis, she was still experiencing daily fatigue and difficulty with exercise.

On exam, AS is a healthy, middle age female. She has normal vitals at rest in addition to benign cardiac and pulmonary exams. She exhibits full range of motion in her extremities. MT has no chronic medical conditions.

Results:

All data points were collected for the rSO2 Nonin sensor, SMO2 Moxy sensor, Temperature, and oxygenation at 60 second intervals, for 4 minutes between 26 to 29 minutes. Initial baseline oxygenation was recorded at time 0:00. rSO2 rose from 55% to 64% throughout the treatment. SMO2 peaked at 97% and remained above 92% for the majority of the treatment. The water oxygenation with Bimini progressively increased from 21.43 to 21.92 during the treatment. Water temperature dropped slowly from 91.6 to 90.4 degrees Fahrenheit.

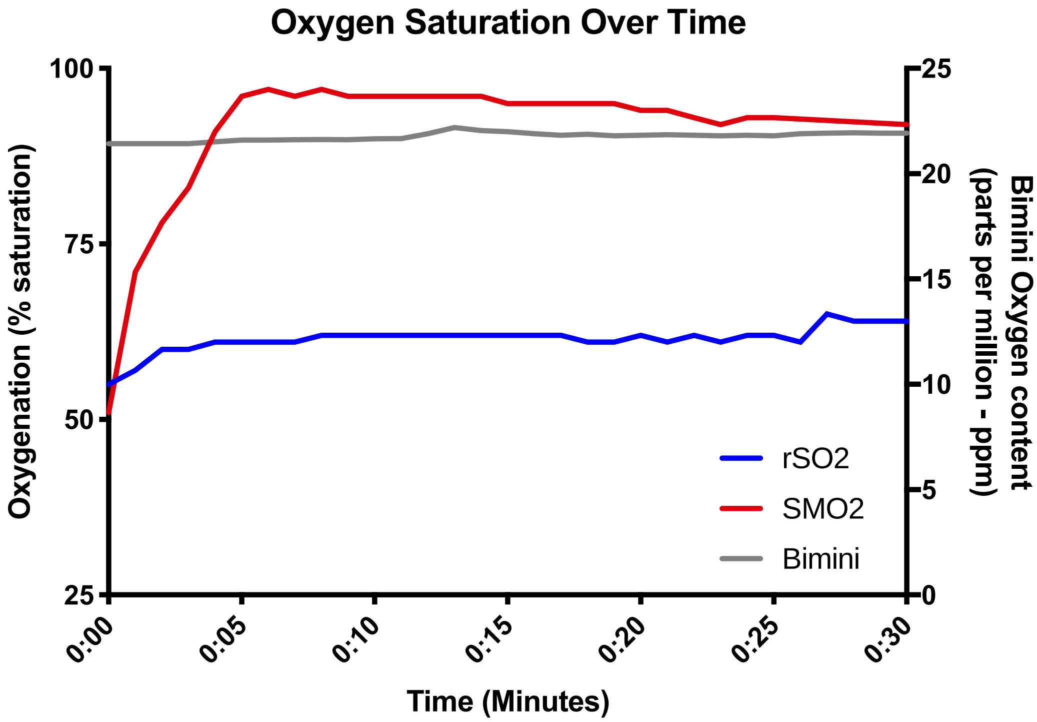

Figure 5: Real time oxygenation values of the right rectus femoris and the left femoral mixed venous sampling (rSO2) utilizing the Moxy and Nonin sensors, respectively. Real time oxygenation values of the bath water used for treatment during the time of Bimini UFB infusion.

Subjectively, AS did not feel any change during the treatment. She experienced no side-effects. After the treatment she did feel an improvement after 24 hours. Her WOMAC score, baseline 8, was 9 at 6 hours and fell to 4 at 24 hours showing an improvement in functioning. Her LEFS score, baseline 62, was 58 at 6 hours and increased to 66 at 24 hours showing an improvement in her daily functionality.

Case 4: SM

Description:

SM is a middle-age male, diagnosed with covid in August of 2020. Prior to diagnosis he was an active adult exercising 3 times a week. He regularly works physically demanding 12-hour shifts. 6 months after diagnosis, he was still experiencing daily fatigue and difficulty with exercise.

On exam, SM is a healthy, middle age male. He has normal vitals at rest in addition to benign cardiac and pulmonary exams. He exhibits full range of motion in his extremities. SM has no chronic medical conditions.

Results:

All data points were collected for SMO2 Moxy sensor, Temperature, and oxygenation at 60 second intervals. rSO2 was not collected. Initial baseline oxygenation was recorded at time 0:00. SMO2, baseline 35, initially dropped to 11 then rose to 88%. After treatment, within 5 minutes, SMO2 had returned to baseline at 36. The water oxygenation with Bimini progressively increased from 14.95 to 17.62 during the treatment. Water temperature dropped slowly from 101.1 to 97.9 degrees Fahrenheit.

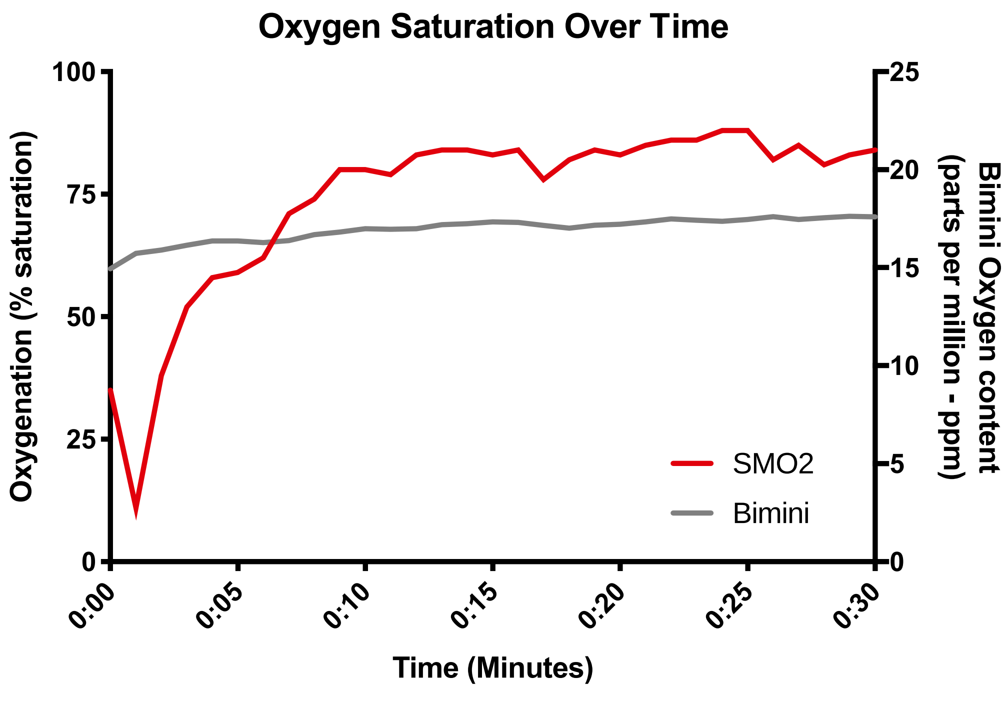

Figure 6. Real time oxygenation values of the right rectus femoris utilizing an SMO2 sensor. Real time oxygenation values of the bath water used for treatment during the time of Bimini UFB infusion.

Subjectively, SM felt a marked improvement during the treatment. He experienced no side-effects. After the treatment he felt an improvement that lasted 6 hours but returned to baseline at 24 hours. His LEFS score, baseline 65, increased to 78 at 6 hours showing an improvement in his functionality but had returned to 65 at 24 hours.

Case 5: SM

Description:

BW is a 45-year-old male, diagnosed with covid in January of 2021. Prior to diagnosis he was an active, retired veteran. He regularly works physically demanding 12-hour shifts as a nurse. 2 months after diagnosis, he was still experiencing daily fatigue, decrease in mental clarity, and difficulty with exercise.

On exam, BW is a healthy, middle age male. He has normal vitals at rest in addition to benign cardiac and pulmonary exams. He exhibits full range of motion in his extremities. SM has no chronic medical conditions.

Results:

All data points were collected for SMO2 Moxy sensor, Temperature, and oxygenation at 60 second intervals. rSO2 was not collected. Initial baseline oxygenation was recorded at time 0:00. SMO2, baseline 58, initially rose to 79%. After treatment, within 5 minutes, SMO2 had returned to baseline at 61. The water oxygenation with Bimini progressively increased from 15 to 16.88 during the treatment. Water temperature dropped slowly from 98.8 to 96.7 degrees Fahrenheit.

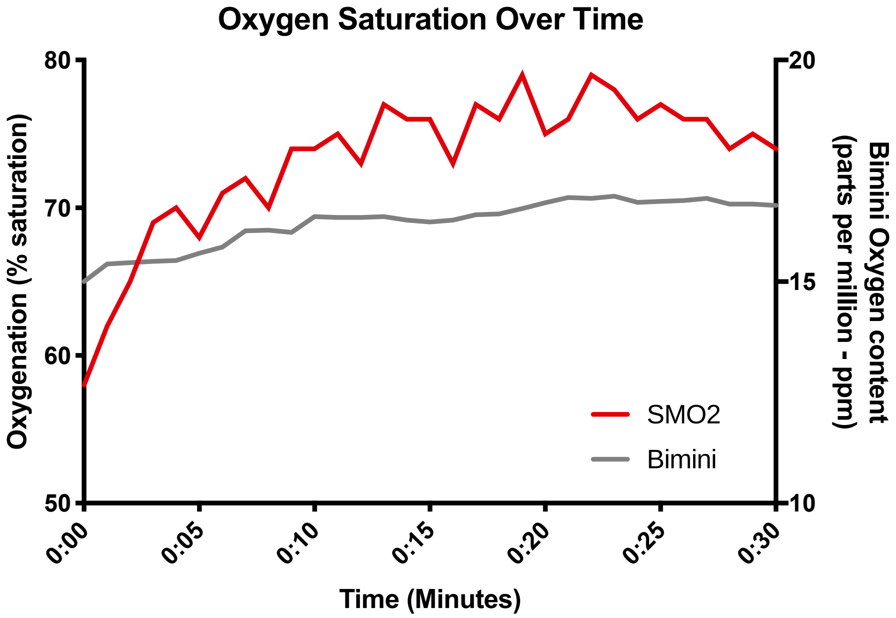

Figure 7. Real time oxygenation values of the right rectus femoris utilizing an SMO2 sensor. Real time oxygenation values of the bath water used for treatment during the time of Bimini UFB infusion.

Subjectively, BW felt better during and right after the treatment. He experienced no side-effects. After the treatment he felt an improvement but at 6 hours and at 24 hours be was fatigued again. His LEFS score, baseline 57, decreased to 50 at 6 hours and 54 at 24 hours.

Discussion:

This study is in line with our prediction that the Bimini Ultra-Fine Bubble (UFB) hydrotherapy, a nanobubble oxygenation technology, will increase muscle oxygen levels acutely and therefore decreased pain, fatigue and recovery from long-covid. Through objective data collected from multiple cases we have shown an increase in muscle SMO2 and mixed venous rSO2 when the Bimini is utilized. Additionally, some of these cases provided subjective data describing an improvement after treatment. Qualitatively, those patients undergoing treatment saw an improvement in their functioning measured by the WOMAC and LEFS scales.

Utilizing the non-invasive technology NIRS, we were able to detect mixed venous blood oxygen saturation of tissues 1-3 cm below the skin by measuring the absorption spectra of the tissue chromophores oxyhemoglobin and deoxyhemoglobin. With most cases, after just 5 to 10 minutes in the Bimini hydrotherapy tub, individuals were increasing their muscle oxygen saturation. rSO2 sampling increased as well. The utilization of both the Moxy device, recording muscle oxygen saturation, and the Nonin device, recording regional oxygen saturation over the femoral vessels, increased our accuracy and made regional oxygen saturation measurements possible.

Utilizing the WOMAC index and the LEFS scale, we saw notable improvements in functionality. The two participants who completed the WOMAC index saw a significant drop in their WOMAC scale (**Figure 5).** Of the four participants who completed the LEFS scale questionnaire before, 6 hours after, and 24 hours after treatment, two saw little change at 6 hours and an improvement 24 hours after treatment (**Figure 6)**. Our fourth patient saw a marked improvement after treatment that lasted at least 6 hours after treatment but had returned to baseline after 24 hours. It is interesting to note that the participant who saw improvements at 6 hours was also the participant who felt subjectively better immediately after the treatment. Future studies should ensure randomization to prevent confounding factors from affecting results.

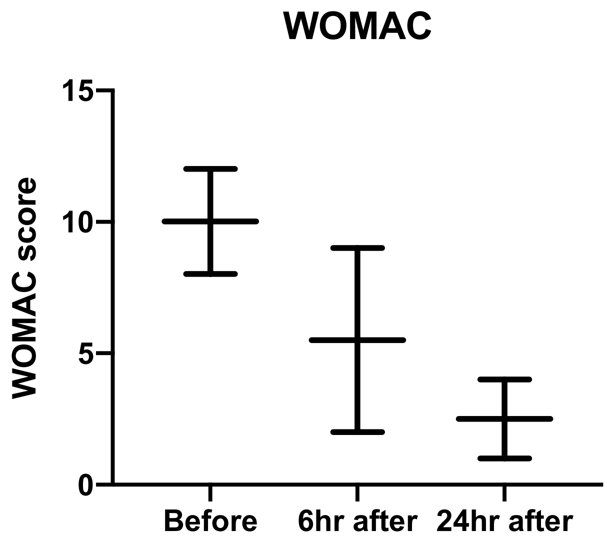

Figure 8: The Western Ontario and McMaster Universities Arthritis Index results before treatment, 6 hours after, and 24 hours after treatment. N=2.

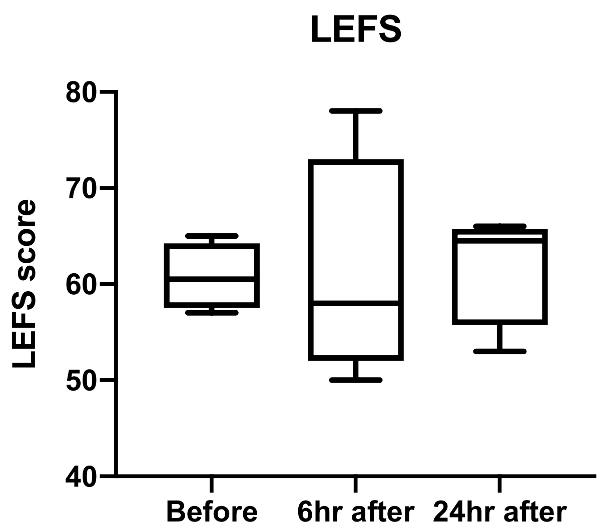

Figure 9: The Lower Extremity Functional Scale questionnaire results before Bimini treatment, 6 hours after, and 24 hours after treatment. N=3.

While previous studies looked at participants who are young and healthy, this was the first study looking at recently recovered COVID-19 patients who experience long-covid sequalae. These findings allude to implications for patients who are septic or hospitalized. Tissue oxygenation hydrotherapy holds a promise for increased recovery, improved performance, improved functionality, illness recovery, and physiologic improvement for those with infections or systemic illnesses.

When combining the data, we saw statistically significant changes in rSO2 and SMO2 at 30 minutes. When looking at the mixed-effects analysis of the rSO2 data, there was a statistically significant fixed effect (type III) with a p value of 0.0164 and a chi-square of 12.86 and matching effect p value of 0.0003. When looking at the mixed-effects analysis of the SMO2 data, there was a statistically significant fixed effect (type III) with a p value of 0.0350, a chi-square of 9.975 and matching effect p value of 0.0016.

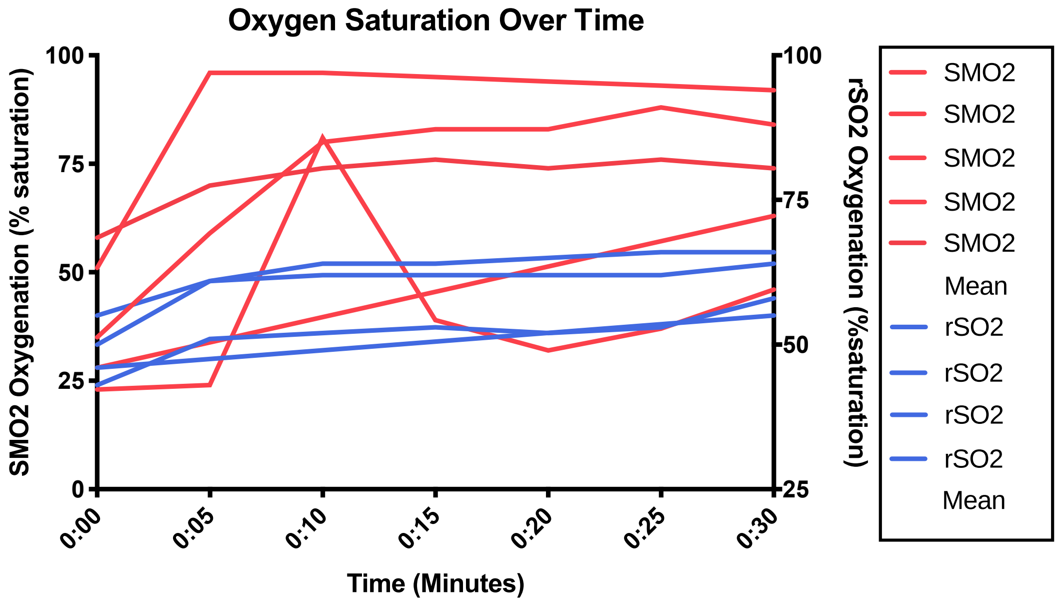

Figure 10: Real time oxygenation values of the right rectus femoris and the left femoral mixed venous sampling (rSO2) utilizing the Moxy and Nonin sensors, respectively for all 5 cases. Dotted lines represent the mean non-linear line of best fit (red – SMO2; blue – rSO2).

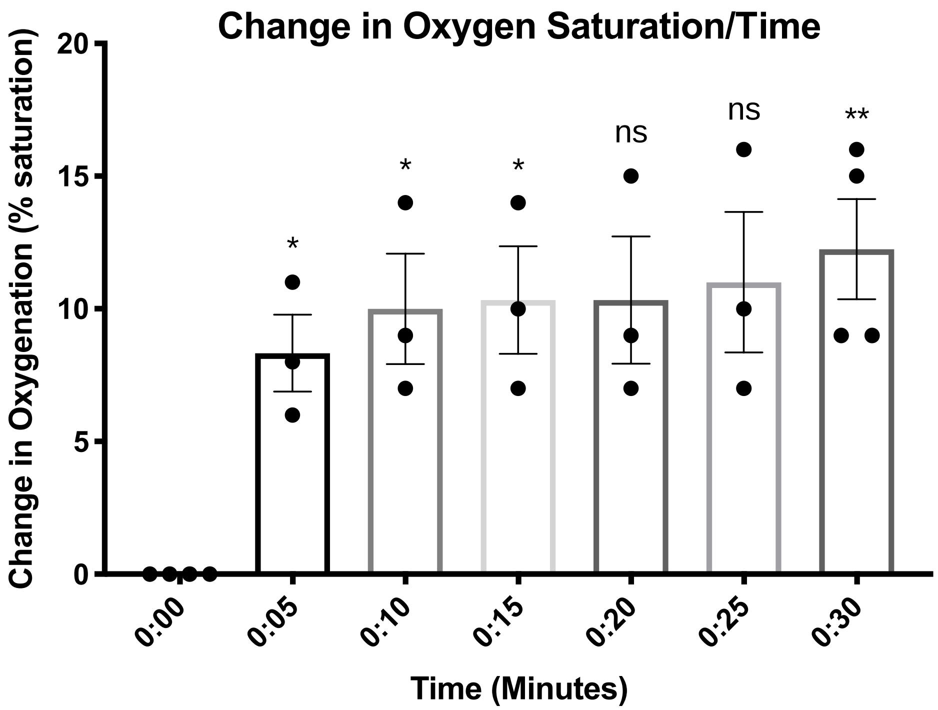

Figure 11: Change in Real time oxygenation values of the left femoral mixed venous sampling (rSO2), n=4.

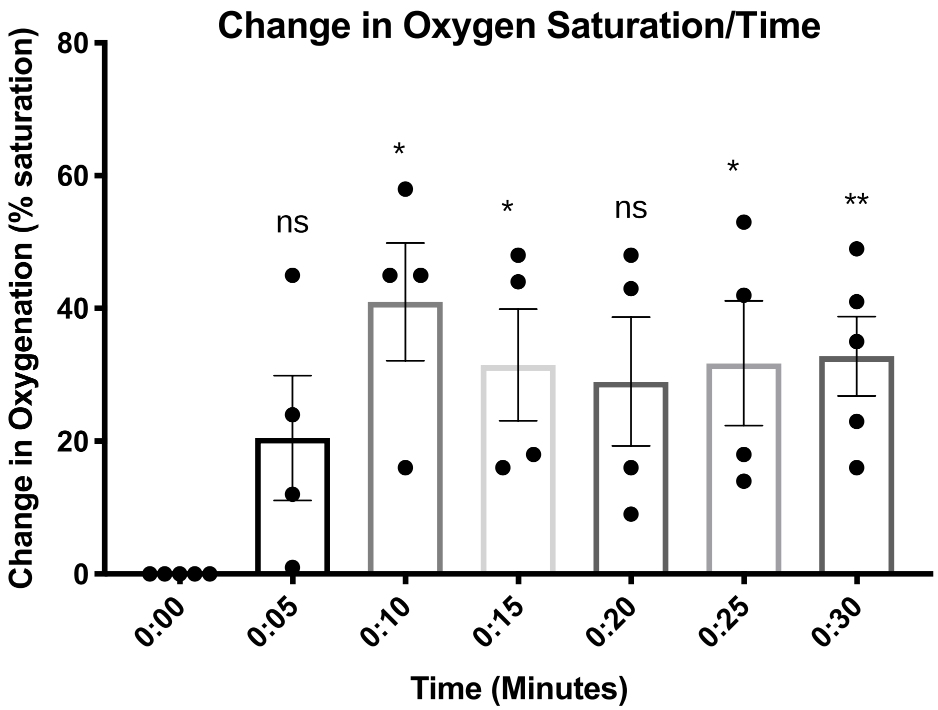

Figure 12: Change in Real time oxygenation values of the right rectus femoris (SMO2), n=5.

Future studies should focus on validating these findings and with a larger sample size, identifying statistically significant changes in oxygenation and subjective functionality. Limitations to this design are the use of subjective questionnaires and the lack of functional testing. With 3 females and 1 male, all middle age, it is impossible to know the extent of confounding factors or gender and/or age-related variations.

Patients who suffered from COVID-19 frequently have long-term side-effects and delayed progression to normal functionality and exercise. Many experience shortness of breath, tachycardia, fatigue, pain after covid taking weeks to months to return to pre-covid health. We know that the smallest decrease in recovery time or temporary improvement in functionality makes a world of difference in patients. From the microscopic level of cellular physiology to the holistic picture of each patient's overall well-being, Bimini UFB provides a new approach to improving recovery utilizing one submicron infusion at a time.

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