Monitored Exercise and Oxygen Therapy Improves Aerobic and Autonomic Function in Post-Acute Sequelae of SARS-CoV-2 Infection (PASC): A Case Series

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Case Report

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Abstract

Case Description: Three females (ages 34, 38, and 38) who contracted COVID-19 in March or April 2020 were treated for post-acute sequelae of SARS-CoV-2 infection (PASC) associated cardiopulmonary and autonomic dysfunction seven to eight months following acute-illness. Exercise tolerance was tested using the Bensen protocol, followed by 22 treatment sessions of graduated treadmill exercise combined with supplemental oxygen two or three times a week, after which the exercise tolerance test was repeated. All patients demonstrated improvement in autonomic function and heart rate response during exercise and demonstrated ~54% improvement in exercise tolerance. Dyspnea remitted or improved in all patients, as did other PASC symptoms, including cough, dyspnea, larynx inflammation, chest tightness, fatigue, and post-exertional malaise.

Discussion: It appears that PASC is a multisystemic, inflammation-mediated condition, that affects the respiratory, cardiac, neurologic, gastrointestinal and autonomic nervous systems, with high variability in symptomatology and course, both between patients and within individuals. Patient safety should be maximized by conducting thorough cardiac, respiratory, neurologic and pre-rehabilitation evaluations to rule out potential complications related to activity and exercise. Clinical course and comprehensive monitoring of heart rate and rhythm, blood pressure, and oxygen saturation should be evaluated before exercise time and intensity is increased, very conservatively.

Summary: Due to the variable nature of PASC, it is crucial to individualize treatment protocols and to modify the protocol based on patient response; however, we show that gradual, monitored exercise combined with supplemental oxygen may improve lingering symptoms and autonomic function in some PASC patients.

Introduction

While the long-term effects of COVID-19 are still not known, it is clear that a substantial percentage of survivors who had experienced even mild-to-moderate acute illness continue to report persistent symptoms for two or more months,[1-3] and many for a year or more. The need for cardiopulmonary-specific rehabilitation for those with post-acute sequelae of SARS-CoV-2 infection (PASC), frequently referred to as “long haulers,” is recognized.[4,5] However, many with PASC also develop dysfunction of the autonomic nervous system,[6] which creates a particular rehabilitation challenge as traditional protocols are often too vigorous for this population, due to abnormal or disproportionate response to exercise, and could potentially even worsen symptoms.

Supplemental oxygen is commonly used as an adjunct to cardiopulmonary rehabilitation and most,[7-10] but not all,[11] clinical trials have found that chronic obstructive pulmonary disease (COPD), pulmonary fibrosis (PF) and other cardiopulmonary patients who receive supplemental oxygen demonstrate a decrease in symptoms, increased exercise tolerance, and improvement in activities of daily living (ADL),

compared to those who do not receive supplemental oxygen. Herein, we present our experience of using progressive treadmill exercise and supplemental oxygen in three female PASC patients.

Case Histories

Patient A

Patient A is 38-year-old Caucasian, female with a past medical history of infrequent childhood seizures, beginning at age eight, which co-occurred with vasovagal syncope between ages 25-30. She also has a history of Lyme Disease, which was diagnosed and treated with IV ozone therapy and supplements in 2018, following symptom onset two years prior. She is a never-smoker.

She contracted COVID-19 in the second week of March 2020, four days after a flight. She tested positive by PCR and subsequently showed the presence of antibodies. She initially experienced cold-like symptoms, including fever (103 F), dyspnea both at rest and exertional, rhinitis, and pharyngitis, followed by an initially productive, then dry cough, nausea, diarrhea, and visual and auditory hallucinations that lasted for approximately three weeks.

Over the next several months she experienced periods of exacerbation and remission, during which, she felt “okay” for a few weeks, followed by worsening dyspnea, chest tightness, anxiety, and panic attacks. She also experienced fatigue and post-exertional malaise, where she felt “good-to-great” during an hour-long walk or yoga class, but then experienced profound fatigue, increased dyspnea, and chest pressure over the subsequent 24-48 hours. She reported mild symptom relief with albuterol sulfate but tried to limit its use due to increased jitteriness. Medications at the time of her initial evaluation included daily hydroxychloroquine, prednisone, Topamax, and Adderall as needed, as well as multiple non-prescription anti-inflammatory supplements.

Patient B

Patient B is a 39-year-old Caucasian, female with a medical history of allergic rhinitis and allergic reaction to penicillin, amoxicillin, and tetracycline. Her psychiatric history includes three hospitalizations in 2002 for medical complications associated with anorexia nervosa, which has been in partial-to-full remission since 2004. She also has a history of persistent depressive disorder, generalized anxiety, specific phobia (in partial remission), and attention-deficit hyperactivity disorder. She was a nationally competitive swimmer, exercised frequently pre-COVID and is a never-smoker.

She contracted COVID-19 in the third week of March 2020, when she began to experience rhinitis, dry cough, and chest tightness. Those symptoms resolved completely three days later, followed by a sudden onset of anosmia, ageusia, and dysgeusia (which lasted until June). On March 23rd she developed a fever (102 F) with intermittent borderline hypothermia (95 F), return of the cough, dyspnea, both on exertion and at rest, chills, and muscle aches, at which time she was clinician diagnosed with COVID-19 as PCR testing was unavailable. She had multiple dermatologic issues including transient hives and “canker-like”

sores that would come and go within hours of initial onset. She also experienced olfactory hallucinations on three occasions.

On April 11, Patient B was admitted to the ER, during which, a chest x-ray revealed “possible mild pleural effusions.” She was discharged without further testing or treatment. Her dyspnea, cough, and fatigue worsened over the next month. She also reported decreased oxygen saturation (low 80’s and high 70’s) after speaking for more than 10-15 minutes or climbing a flight of stairs, which coincided with heart rate lability (154 to 40 within 60 seconds). Other symptoms included brain fog, impaired memory, nightmares, and night sweats. She had two more ER admissions in June for oxygen desaturation upon exertion, dyspnea, persistent fever, and chest pain, at which time she was diagnosed with hypertension. Her last ER admission, in late July, was for chest pain which, at the time, was attributed to a cough-induced muscle strain. Pulmonary function tests, echocardiogram, and cardiac stress test were all normal. Holter monitor showed inappropriate sinus tachycardia. She continued to experience daily fevers (99.5-102) until early October.

Medications at the time of her initial evaluation included Zoloft, Adderall XR, and TriNessa Lo daily, as well as Singulair (for allergic rhinitis), trazadone, and albuterol as needed. After her evaluation she was diagnosed with coronary vasospasms for which daily Procardia XL was prescribed.

Patient C

Patient C is 34-year-old, Black, female who has a medical history significant for sickle-cell trait (carrier only), HSV-1, and a childhood history of Tourette's syndrome (in remission). She is a runner and never-smoker.

Patient C began experiencing dyspnea on April 17, 2020 and was clinician diagnosed with COVID-19 in the emergency department the following day, but subsequently released without treatment. Although her oxygen saturation remained ≥ 98%, she continued to experience dyspnea with suspected pneumonia in the months that followed, even as she was able to work and run 1-2 miles several times each week. An August CT scan was "mostly normal," but showed some post-viral inflammation and a vascular assessment of that same CT scan found “damage to approximately 30%of a group of smaller blood vessels in the lungs.”

In early August, Patient C experienced severe laryngeal spasms for seven days, after using albuterol and Advair. She discontinued those medications but continued to experience persistent inflammation in her throat and larynx. A January CT scan was normal with the exception of mildly dilated distal esophagus. After endoscopic evaluation was normal, her ENT suggested her symptoms might indicate irritable larynx syndrome and/or possible nerve damage.

Medications at the time of Patient C’s initial evaluation included Albuterol, Advair Naproxen, Celebrex, and non-prescription supplements.

TREATMENT

All three patients underwent pre- and post-rehabilitation exercise testing using the Bensen treadmill protocol.[12] Resting heart rate and rhythm via ECG, blood pressure, and oxygen saturation were measured pre-exercise, at each stage of testing, and during recovery. Rate of Perceived Exertion (RPE) and Breathlessness[13] were obtained at peak exercise. The patients walked on the treadmill at an initial speed of 1.0 MPH with a 0% incline (1.77 METs) for two minutes. Intensity was then increased by approximately 25% every two minutes, alternating between speed and incline. The test was terminated when age-adjusted (200 - age) heart rate maximum was reached, or moderate symptom burden was reported.

Patients underwent two (Patients A & C) or three (Patient B) exercise sessions per week for a total of 24 sessions. Initial treatment sessions were approximately 25% longer in duration and lower in intensity, such that 80-100% of peak exercise tolerance was achieved within three sessions. In subsequent sessions, time and intensity were increased by no more than 0.5 METS, as tolerated based upon vital signs and patient-reported symptoms since previous session and during exercise. The patients received 6 liters per minute of continuous oxygen via nasal cannula regardless of oxygen saturation 5 minutes prior to, during, and 5 minutes post-exercise.

Findings

Physiological Measures

All three patients demonstrated improvement in exercise tolerance, autonomic function, and resting and exercise heart rate at each stage. Heart rate and blood pressure readings at each pre- and post-treatment testing exercise stage are displayed in Figure 1. For each session, peak MET, heart rate and blood pressure at rest, peak exercise, and recovery for each patient can be found in the supplementary materials (Figures, Supplementary Digital Content 1, 2 and 3). Pre- and post-testing results are displayed in Table 1.

Post-program, patients A and B were able to tolerate 18 minutes of treadmill exercise at a peak intensity of 3.7 mph with a 13% incline. This translates into a workload of 10.47 METs compared to 6.82 METs upon initial testing and represents an improvement of 53.5%. Patient C was able to tolerate 20 minutes of treadmill exercise at a peak intensity of 4.7 mph with a 13% incline, which translates into a workload of 13.0 METs as compared to 8.43 METs upon initial testing, and 54.2% improvement.

PASC Symptoms

Post-treatment, Patient A's dyspnea, chest tightness, fatigue, and post-exertional malaise had significantly improved. Patient B reported significant improvement in her cough and cognitive function, with near remission of dyspnea, night sweats, and nightmares. She continues to experience fevers a few times a month, typically triggered by stress or physical activity, but the temperature spikes are now rarely above 99.5 and they last minutes instead of the hours they occurred previously. Her regular body temperature has also returned to her pre-COVID-19 temperature (~97.5 F). Patient C reported near-remission of dyspnea and more gradual but continuing improvement in throat and larynx inflammation.

Discussion

It is widely-believed that PASC is a multisystemic, inflammation-mediated condition, known to affect the respiratory, cardiac, neurologic, gastrointestinal and autonomic nervous systems.[1] The present report describes successful use of progressive treadmill exercise combined with supplemental oxygen to treat PASC-associated cardiopulmonary and autonomic dysfunction. While research is limited, we recognize that PASC symptomatology and course are highly variable, both between patients and within individuals. As such, patient safety should be maximized through a thorough cardiac, respiratory, and neurologic evaluation and clearance, as well as a thorough pre-rehabilitation assessment to rule out potential complications related to activity and exercise. In addition, clinical course and comprehensive pre-, intra- and post-treatment monitoring of heart rate and rhythm via ECG, blood pressure, oxygen saturation should be evaluated and exercise time and intensity should be increased very conservatively. The potential for post-exertional malaise (PEM) or exacerbation of symptoms should also be closely monitored.

Current recommendations regarding the use of graded exercise in PASC rehabilitation range from initiating exercise therapy only after the patient has been symptom free for at least two weeks[14] to beginning a structured aerobic and resistance training program.[15] Due to the variable nature of PASC, one rehabilitation protocol will not work for every patient and any treatment plan needs to be adjusted constantly for each individual.

It has been proposed that COVID-19 might be associated with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS),[16] for which the appropriateness of graded exercise therapy is controversial.[17,18] However, findings from a recent study that compared the autonomic functions of PASC patients with and without fatigue showed that autonomic dysfunction in both groups differed from that previously observed in ME/CFS,[19] suggesting that while they share similar features they are not the same syndrome. Furthermore, combining supplemental oxygen with treadmill exercise reduces stress of the physical activity on the body, and our early success with its use provides support for conducting larger clinical trials to test the efficacy of graded treadmill exercise with supplemental oxygen for treatment of PASC as well as ME/CFS and other syndromes with overlapping symptoms.

Hyperinflammation, potentially mediated by mast cell activation, has also been proposed as one potential mechanism underlying PASC.[20] As such, we recommend a substantially less vigorous exercise protocol including breathwork, relaxation training and meditation with patients who are in this hyperinflammatory state, as we have found that even minimal physical exertion (e.g. walking up a flight of stairs), emotional upset, and cognitive stress can exacerbate symptoms. However, once hyperinflammation subsides, very gradual, carefully monitored exercise combined with supplemental oxygen may improve patients lingering symptoms and autonomic function.

Summary

In conclusion, graduated treadmill exercise combined with supplemental oxygen may improve exercise tolerance and symptoms in PASC patients. Still, a one-size-fits-all approach will not be helpful to all PASC patients and may be harmful to some. Individualized, flexible treatment plans are recommended, as is further research of treatment described here and individual differences in treatment response.

Declarations

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Conflict of Interest Disclosure: Noah Greenspan is the Founder of the Pulmonary Wellness Foundation and Post-COVID Rehabilitation & Recovery Clinic at H&D Physical Therapy. He also serves as a consultant for PulmonX. Gregory Hullstrung is a Partner at H&D Physical Therapy.

All authors have read and approved the submitted manuscript.

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Tables

Table 1. Pre- and Post-Treatment Exercise Tolerance Test Results for Patients A, B, and C

	Patient A		Patient B		Patient C	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
Time	14:00 (Stage 7)	18:00 (Stage 9)	14:00 (Stage 7)	18:00 (Stage 9)	16:00 (Stage 8)	20:00 (Stage 10)
Peak speed (MPH)	2.9	3.7	2.9	3.7	3.7	4.7
Peak incline (% Grade)	9%	13%	9%	13%	9	13%
Peak MET level	6.82	10.47	6.82	10.47	8.43	13.00
Peak heart rate	128	137	157	138	150	174
Peak blood pressure	128/60 mm Hg	146/72 mm Hg	180/102 mm Hg	166/100 mm Hg	168/72 mm Hg	176/84 mm Hg
Lowest O_2 saturation	96	97	97	96	97	99
Peak rate of perceived exertion	12 (Between Fairly Light and Somewhat Hard)	13 (Somewhat Hard)	15 (Hard)	13 (Somewhat Hard)	15 (Hard)	15 (Hard)
Peak breathlessness	13 (Somewhat Strong)	13 (Somewhat Strong)	15 (Strong)	11 (Fairly Mild)	15 (Strong)	13 (Somewhat Strong)

Figures

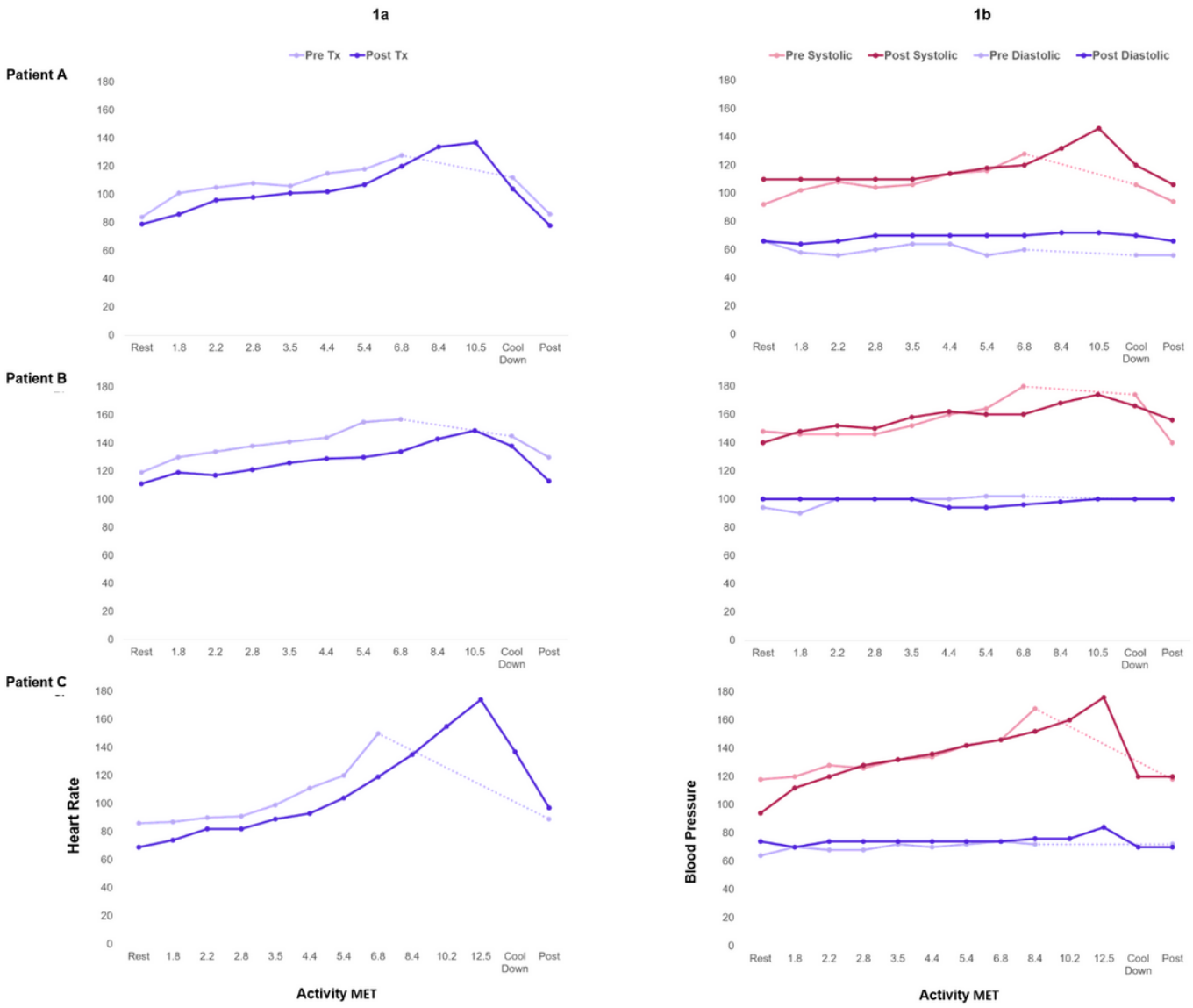

Figure 1

Pre- and Post-Treatment Heart Rate and Blood Pressure (mm Hg) at Rest, During the Exercise Tolerance Test, and Five minutes Post-Exercise for Patients A, B, and C. a) Light purple indicates pre-treatment heart rate and dark purple shows heart rate post-treatment; b) Systolic readings are presented in red and and diastolic readings are presented in purple Light red/purple indicates pre-treatment bood pressure and dark red/purple shows blood pressure post-treatment.

Supplementary Files

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- SupplementaryAppendicesandFigureLegends.docx