

Molecular Hydrogen as an Adjuvant Therapy May be Associated with Increased Oxygen Saturation and Improved Exercise Tolerance In a COVID-19 patient

Tyler LeBaron¹, Ram Singh², Ghazi Halabi³, Ghizal Fatima⁴, Richa Rai⁵, and Alex Tarnava⁶

¹Southern Utah University

²Halberg Hospital and Research Institute

³Halberg Chrono-Cardiology Center

⁴Era Medical College

⁵School of Physiotherapy, Delhi Pharmaceutical Sciences and Research University

⁶Drink HRW

September 25, 2021

Abstract

COVID-19 is associated with respiratory failure and subsequent hypoxia. New therapies that reduce hypoxia are urgently needed. Molecular hydrogen (H₂) therapy may reduce inflammation, oxidative stress, and hypoxia. This case report suggests that hydrogen-rich water (HRW) increases oxygen saturation increase exercise tolerance in a patient with COVID-19-like symptoms.

Molecular Hydrogen as an Adjuvant Therapy May be Associated with Increased Oxygen Saturation and Improved Exercise Tolerance In a COVID-19 patient

Ram B Singh¹, Ghazi Halabi², Ghizal Fatima³, Richa H Rai⁴, Alexander T. Tarnava⁵, *Tyler W. LeBaron^{6,7,8}

¹Halberg Hospital and Research Institute, Moradabad, India.

²Halberg Chrono-Cardiology Center, Aley, Lebanon.

³Era Medical College, Lucknow, India.

⁴School of Physiotherapy, Delhi Pharmaceutical Sciences and Research University Delhi, India.

⁵Drink HRW, New Westminster, BC, Canada

⁶Centre of Experimental Medicine, Institute for Heart Research, Slovak Academy of Sciences, Faculty of Natural Sciences of Comenius University, 84104 Bratislava, Slovak Republic

⁷Molecular Hydrogen Institute, Cedar, UT 84720, USA

⁸Department of Kinesiology and Outdoor Recreation, Southern Utah University, Cedar, UT 84720, USA

*Corresponding Author:

Tyler W. LeBaron email: tylerlebaron@suu.edu

ABSTRACT

COVID-19 is associated with respiratory failure and subsequent hypoxia. New therapies that reduce hypoxia are urgently needed. Molecular hydrogen (H₂) therapy may reduce inflammation, oxidative stress, and hypoxia. This case report suggests that hydrogen-rich water (HRW) increases oxygen saturation increase exercise tolerance in a patient with COVID-19-like symptoms.

Keywords : Antioxidant, free radical stress, inflammation, hydrogen-rich water, post-COVID-19

Key Clinical Message

Administration of molecular hydrogen dissolved in water to patient with COVID-19-like symptoms may improve oxygen levels and exercise capacity.

1. INTRODUCTION

Recent studies indicate that severe acute respiratory syndrome can develop from novel coronavirus (SARS-CoV-2), which may cause COVID-19.^{1, 2} The clinical features of SARS-CoV-2 infection may range from silent infection to serious illness including death.^{1, 2} The disease is associated with pneumonia and consolidation in the lower and upper lungs that lead to respiratory failure with hypoxia.^{1, 2} Computerized tomography of the thorax may reveal a ground glass appearance of lungs, indicating viral pneumonia. There is an unmet need to develop new therapies for this disease, because COVID-19 spreads rapidly, resulting in a pandemic with limited agents for treatment. In serious patients with COVID-19, respiratory failure results in hypoxia, which is characterized by a lower oxygen saturation in the blood circulation.^{1, 2} Long term consequences of COVID-19 include symptoms such as fatigue, headaches, joint pain and dyspnea, as well as other neurological, lung, and heart damages.³ A recent WHO sponsored randomized trial following 11,330 adults across 30 countries and 405 hospitals found that the repurposed anti-viral drugs remdesivir, hydroxychloroquine, interferon and lopinavir or the combination of interferon and lopinavir had little to no impact on mortality.⁴ High doses of cortisone have been found to be useful among these patients.⁵ Mutations to the SARS-CoV-2 virus have created uncertainties regarding some treatment options, with recent research suggesting that monoclonal antibody therapies may be less effective against the emerging Delta variant.⁶

Recently, molecular hydrogen (H₂) has been suggested for the treatment of COVID-19, due to its potential antioxidant and anti-inflammatory effects.^{7, 8} It is hypothesized that H₂ therapy may decrease inflammation by decreasing the cytokine storm and by reducing free radical-induced damage, which may decrease hypoxia and delay the need for oxygen therapy.⁷⁻¹¹ This hypothesis has led to the initiation of a large-scale multicenter trial in Europe utilizing hydrogen-producing tablets in high-risk patients undergoing ambulatory care.¹² The concept that molecular hydrogen may be a beneficial treatment for severe COVID-19 is supported by a small trial in China that reported hydrogen inhalation was effective for reducing disease severity and dyspnea.¹³ Further, before undergoing this case report, the authors received private correspondence regarding the potential effectiveness of hydrogen-producing tablets in a small, randomized placebo-controlled trial with COVID-19 patients (n=24). Administration of four hydrogen-producing tablets per day led to a significant reduction in interleukin-6 (IL-6) and fatigue (Sergej Ostojic MD, PhD, email correspondence May 7th, 2021). Here we report that molecular hydrogen, administered as hydrogen-rich water (HRW), may increase oxygen saturation in the blood circulation and increase exercise tolerance.

2. CASE REPORT

2.1. Background

A male physician aged 77 years, presented with COVID-19 like symptoms, potentially as a manifestation of side effects from the “Covishield” vaccination, developed by Oxford-AstraZeneca, on April 17, 2021. Further details of this patient regarding clinical presentation and treatment given in acute stage have been reported earlier.¹⁴ After recovery from acute phase pneumonia consistent with COVID-19 patients, this patient developed chronic hypoxia with oxygen saturation between 91%-93%. In the first week of June 2021, (6 weeks after the acute phase of symptoms), his total and differential blood counts, as well as platelet counts, were within normal limits. His Hb level was 11.2 g/dL, aspartate aminotransferase (AST) 42.0 IU/L (normal

up to 40 IU), and ferritin 305.60 ng/mL. His C-Reactive protein (CRP) was 7.41 mg/L (normal, 0.0 to 6.0 mg/L), D Dimer 248.2 ng/mL (normal < 500 ng/mL), and IL-6, was 4.21 pg/mL (normal 0.0 to 0.5 pg/mL).

In view of the continuation of respiratory failure with hypoxia due to fibrosis of the lungs, his oxygen saturation at rest was 92% to 93%. Four weeks post-vaccination his echocardiogram revealed that his ejection fraction was >65% and there was no evidence of cardiac dilatation. Breathing exercises with emphasis on abdominal breathing was the main stay of treatment. Nebuliser with asthalin + budicort + evolin were continuously and regularly administered twice daily. There was marked recovery after 6 weeks of treatment, but high-resolution computerized tomography showed haziness in lower lung zones, indicating damage similar to post-COVID-19 fibrosis. Due to the presence of persistent fibrosis of the lungs, he was administered Nintedanib soft gelatin capsules 100 mg twice daily for 45 days, beginning 15 days after the onset of symptoms. He continued taking coenzyme Q10 (CoQ10) 200 mg twice daily, apaxivan, and rosuvastatin 5 mg daily.

2.2. Hydrogen Intervention

However, despite the treatment there was still no improvement in oxygen saturation. Therefore, in addition to the above treatment, he was also administered HRW by using H₂-producing, magnesium-based tablets (three tablets in the morning and two in the evening). Each tablet was dissolved in 200 mL of water, for a total daily intake of 1L of HRW. Hydrogen concentration was estimated at 16 mg/L based on extrapolation from available gas chromatography data on the hydrogen tablets obtained via H₂ Analytics (Las Vegas, USA) using gas chromatography (SRI 8610C; California, USA), giving a total daily dose of [?]16 mg of molecular hydrogen per day. The effect of HRW treatment was assessed by measuring SpO₂ levels before (0 min) and 5, 30, 45, and 60 min after treatment using the oximeter and multipara monitor. To assess the effects of combined exercise and HRW the patient was advised physical training prior to HRW treatment. The exercise protocol was slow jogging for approximately two minutes and repeated three times with 3-5 min rest between. However, due to a marked decline in SpO₂ levels of 81-84%, the exercise could not be completed. Therefore, the exercise was done immediately after HRW treatment and SpO₂ level was monitored during and after exercise at the same time intervals (5, 30, 45, and 60 min).

3. RESULTS

Treatment with H₂ was associated with significant changes in the oxygen saturation as measured via oximeter and multipara monitor (Fig. 1). Five minutes after H₂ treatment in the morning, mean oxygen saturation measured over the five-day period increased from 92.6% to 97.2%, and then slowly decreased to 96.4%, 95%, and 93.4% after 30, 45, and 60 min, respectively (Fig. 1A). Evening H₂ treatment increased mean oxygen saturation from 92.6% to 96% after 5 min. After 30, 45, and 60 min mean oxygen saturation was 95.4%, 94.4%, and 92.6%, respectively (Fig. 1B).

Fig 1. Mean oxygen saturation following five-day treatment with HRW. (A) treatment with three H₂-producing tablets in the morning; (B) treatment with two H₂-producing tablets in the evening. Hydrogen-producing tablets were dissolved in 200 mL of water each for a total daily intake of 1L of HRW. The results are presented graphically as mean \pm SD with individual values for each daily measurement. * p < 0.05, ** p < 0.01, *** p < 0.001 as compared to 0 (before treatment). Statistical differences were analyzed using repeated measure one-way Analysis of Variance (ANOVA), followed by Tukey's Multiple Comparison Test using GraphPad Prism Software, ver. 8.0.2. (GraphPad Software, San Diego, USA).

The effect of HRW treatment followed by exercise on oxygen saturation is presented on Fig.2. Regular HRW treatment with subsequent exercise increased basal oxygen saturation (measured before HRW administration) from 83% on day 1 to 90% on day 10. An additional marked increase in exercise tolerance was observed after 5, 30, 45, and 60 min on each day of the treatment, with the most prominent effect detected after 30 minutes (oxygen saturation ranged from 94% on day 1 to 96% on day 10).

Fig. 2. Time course of oxygen saturation after daily HRW treatment followed by exercise. The baseline SpO₂ measurements (0 min) were performed just prior to HRW treatment.

4. DISCUSSION

This case report reveals that treatment with HRW was dose-dependently associated with a significant increase in oxygen saturation within 5 min of therapy in a patient with symptoms consistent with post-acute COVID-19-like side effects such as subacute to chronic hypoxia (Fig. 1). The findings also reveal that treatment with HRW may have increased exercise tolerance from hypoxia to near normal oxygen saturation (Fig. 2).

Molecular hydrogen has shown to protect the lungs from hypoxia/re-oxygenation injury in mice by lowering free radical and inflammatory damages.¹⁵ Similar benefits were seen in a recent multicenter clinical trial utilizing hydrogen gas inhalation for chronic obstructive pulmonary disease (COPD).¹⁶ Hydrogen therapy improved breathlessness, cough, and sputum scale (BCSS) as compared to placebo. However, in this multicenter trial there was no improvement in SpO₂ in the hydrogen group as compared to the placebo group and change from baseline. Nevertheless, there were time by group interactions with respect to the changes from baseline in SpO₂ ($p < 0.0001$).¹⁶ In data obtained via private correspondence, hydrogen water prepared via hydrogen-producing magnesium tablets led to significantly lower fibrinogen levels ($p = 0.03$), prothrombin time ($p = 0.02$) and INR ($p = 0.03$) in COVID-19 patients complicated with pneumonia, although this data set was from only five patients, so no concrete conclusions can be drawn (Sergej Ostojic MD, PhD, email correspondence May 7th, 2021). Additionally, similarly prepared HRW demonstrated a significant improvement in VO₂ and various exercise indices in middle-aged overweight women after 28 days intake.¹⁷ Similarly, a lower dosage of ~2 mg/day for 14 days also demonstrated improvements in peak oxygen uptake.¹⁸ Overall, hydrogen therapy has shown significant promise as an ergogenic agent for improved exercise performance and recovery.¹⁹ No study is available on the role of hydrogen showing increased oxygen saturation among patients with hypoxia or border line lower oxygen saturation, in COVID-19 or from any other cause. Therefore, direct comparisons between this case report and the established literature are not possible.

In energy metabolism, the heart acts robustly, with the highest uptake of oxygen in the tissues (~0.01 mL O₂*g⁻¹*min⁻¹). The heart needs ~6 kg of ATP per day, which is 15–20 times its own weight.²⁰ During hypoxia there is an imbalance between oxygen demand and oxygen supply. The heart is under challenge during chronic hypoxia to produce optimal amount of ATP with limited O₂ for contraction and maintenance of physiological cardiac function.^{20–22} The heart consumes a substantial amount of energy and it is important to maintain the balance of energy supply and demand when oxygen is limited.²¹ Previous studies showed that the heart switches from fatty acid to glucose utilization to maintain metabolic efficiency in the adaptation to chronic hypoxia.^{21, 22} Molecular hydrogen can attenuate allergic inflammation by preventing this pathological metabolic switching from mitochondrial oxidative phosphorylation to glycolysis from occurring.²³

Human studies have demonstrated that chronic consumption of hydrogen water may lower heart rate in subjects with metabolic syndrome ($n = 60$, 24 weeks),²⁴ and acutely lower heart rate during strenuous exercise.²⁵ Conversely another study reported that hydrogen water consumption has a heart rate raising effect in women observed at rest.²⁶ Importantly, molecular hydrogen has shown to potentiate the beneficial post-infarct effects of hypoxic conditioning on rat hearts^{27, 28} and has shown to ameliorate the deleterious effects of intermittent hypoxia in rodent models.^{28–32}

It seems that hydrogen therapy as HRW, may be an effective and novel adjuvant treatment against acute and post-acute COVID-19. COVID-19 is associated with cytokine storm and multiple organ damage through many mechanisms.^{1, 2} The exact molecular mechanism of how hydrogen therapy provides benefits to COVID-19 patients is not known. Hydrogen may induce the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, thereby exerting cytoprotective activity resulting in decreased damage to cells caused by SARS-CoV-2 infection.^{1, 8, 14} It is also possible that SARS-CoV-2 induces activation of apoptosis and protein 53 (p53) signaling pathway in lymphocytes, and hydrogen could exert anti-apoptotic effects in lymphocytes by decreasing p53. This may reduce disease progression and be used for prevention and treatment in COVID-19 patients.⁸ Hydrogen supplementation can suppress the elevation of pro-inflammatory proteins (e.g., tumor necrosis factor- α , IL-1b, IL-6, IL-10 and intercellular cell adhesion molecule-1) via nuclear factor kappa-light chain-enhancer of activated B cells (NF κ B) pathway.⁸ It is known that these pro-inflammatory cytokines are overexpressed in COVID-19 infection and they play important roles in the progression of multi-organ failure.

Fatigue remains a common reported side effect of acute COVID-19, with chronic fatigue being reported as one of the most common side effects of post-acute COVID-19.³³ HRW as delivered by hydrogen-producing magnesium tablets has shown to improve alertness equivalent to caffeine in a head-to-head crossover study in young, healthy, sleep-deprived individuals (n=23).³⁴ Additionally, HRW was shown to result in a more robust stimulation of brain metabolism compared to caffeine, as measured via MRI, in a double-blinded, placebo-controlled RCT in young, healthy sleep deprived individuals.³⁵ Molecular hydrogen was also shown to reduce both temporary and prolonged fatigue,³⁶ suggesting it could be effective in eradicating post-acute COVID-19 weakness.

Lastly, hydrogen therapy may be useful adjuvant to other intervention agents because it has potential to reduce free radical-induced damage and inflammation. Hydrogen water has demonstrated the ability to potentiate conventional pharmaceutical treatments, showing additional or even synergistic effects with sulfasalazine in a colitis model in mice,³⁷ with 5-FU in a colorectal cancer model in mice,³⁸ with minocycline in treating post-ischemic stroke rats,³⁹ and of hydrogen water and photobiomodulation in Parkinson's disease patients.⁴⁰

5. CONCLUSIONS

Treatment with HRW may enhance oxygen saturation in patients with hypoxia, as presented in this case study. Hydrogen therapy may also enhance exercise tolerance resulting in significantly lower episodes of hypoxia during physical training. It is proposed that hydrogen supplementation may produce selective anti-oxidation, anti-inflammation, anti-apoptosis, favorable gene expression alterations, and act as a therapeutic gaseous-signal modulator.

Hydrogen-rich water may exert protective effects on individuals experiencing symptoms consistent with post-acute COVID-19, whether induced by viral infection or as a rare adverse event experienced by vaccination. Well-controlled clinical trials are needed to confirm this preliminary case report.

Acknowledgements

We express our gratitude to the International College of Nutrition for providing logistic support and to Mr. Alex Tarnava, Drink HRW, Coquitlam, Canada for providing financial support and hydrogen-producing magnesium tablets for this case.

Author contribution

RBS, GH, GF, and RHR were involved in concept/design and data collection. RBS, ATT, and TWL wrote the article. All authors read and approved the final version of the manuscript.

Conflict of interest

AT is involved in commercial entities with interest in the marketing of hydrogen-rich water. TWL has received travel reimbursement, honoraria, and speaking and consultancy fees from various academic and commercial entities regarding molecular hydrogen. All other authors report no conflict of interest.

REFERENCES

1. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *New England Journal of Medicine*. 2020;382(18):1708-20. [10.1056/NEJMoa2002032](https://doi.org/10.1056/NEJMoa2002032)
2. Salje H, Tran Kiem C, Lefrancq N, Courtejoie N, Bosetti P, Paireau J, et al. Estimating the burden of SARS-CoV-2 in France. *Science*. 2020;369(6500):208. [10.1126/science.abc3517](https://doi.org/10.1126/science.abc3517)
3. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Scientific Reports*. 2021;11(1):16144. [10.1038/s41598-021-95565-8](https://doi.org/10.1038/s41598-021-95565-8)

4. Pan H, Peto R, Karim QA, Alejandria M, Henao-Restrepo AM, García CH, et al. Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results. medRxiv. 2020:2020.10.15.20209817. *10.1101/2020.10.15.20209817*
5. Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020;324(13):1330-41. *10.1001/jama.2020.17023*
6. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature. 2021;596(7871):276-80. *10.1038/s41586-021-03777-9*
7. Yang F, Yue R, Luo X, Liu R, Huang X. Hydrogen: A Potential New Adjuvant Therapy for COVID-19 Patients. Front Pharmacol. 2020;11:543718-. *10.3389/fphar.2020.543718*
8. Wang M, Peng J, Hui J, Hou D, Li W, Yang J. Hydrogen therapy as an effective and novel adjuvant treatment against COVID-19. QJM. 2021;114(1):74-5. *10.1093/qjmed/hcaa301*
9. Ge L, Yang M, Yang N-N, Yin X-X, Song W-G. Molecular hydrogen: a preventive and therapeutic medical gas for various diseases. Oncotarget. 2017;8(60):102653-73. *10.18632/oncotarget.21130*
10. Russell G, Rehman M, LeBaron TW, Veal D, Adukwu E, Hancock J. An overview of SARS-CoV-2 (COVID-19) infection and the importance of molecular hydrogen as an adjunctive therapy. Reactive Oxygen Species. 2020;10(28):150-65.
11. LeBaron T, McCullough M, Ruppman SK. A novel functional beverage for COVID-19 and other conditions: Hypothesis and preliminary data, increased blood flow, and wound healing. Journal of Translational Science. 2019;6:1-6. *10.15761/JTS.1000380*
12. ClinicalTrials.gov. Evaluation of the Daily Intake of 0.5 L of Water Saturated With Molecular Hydrogen for 21 Days in COVID-19 Patients Treated in Ambulatory Care (HYDRO COVID) 2021 [updated May 27, 2021; Accessed 2021 July 30]. Available from: <https://clinicaltrials.gov/ct2/show/NCT04716985>.
13. Guan W-J, Wei C-H, Chen A-L, Sun X-C, Guo G-Y, Zou X, et al. Hydrogen/oxygen mixed gas inhalation improves disease severity and dyspnea in patients with Coronavirus disease 2019 in a recent multicenter, open-label clinical trial. J Thorac Dis. 2020;12(6):3448-52. *10.21037/jtd-2020-057*
14. Singh RB, Agarwal V, Agarwal A, Elkilany G, Zayed O, Gupta R, et al. Can Vaccination Misguide and Masquerade as Covid-Induced Heart Failure and Lung Failure? World Heart Journal. 21;13(3).
15. Chen M, Zhang J, Chen Y, Qiu Y, Luo Z, Zhao S, et al. Hydrogen protects lung from hypoxia/re-oxygenation injury by reducing hydroxyl radical production and inhibiting inflammatory responses. Scientific Reports. 2018;8(1):8004. *10.1038/s41598-018-26335-2*
16. Zheng Z-G, Sun W-Z, Hu J-Y, Jie Z-J, Xu J-F, Cao J, et al. Hydrogen/oxygen therapy for the treatment of an acute exacerbation of chronic obstructive pulmonary disease: results of a multicenter, randomized, double-blind, parallel-group controlled trial. Respir Res. 2021;22(1):149-. *10.1186/s12931-021-01740-w*
17. Ostojic S, Korovljev D, Štajer V, Javorac D. 28-Days Hydrogen-Rich Water Supplementation Affects Exercise Capacity in Mid-Age Overweight Women: 2942 Board #225 June 1 3. Medicine & Science in Sports & Exercise. 2018;50:728-9. *10.1249/01.mss.0000538402.25953.d2*

18. Hori A, Sobue S, Kurokawa R, Hirano S-i, Ichihara M, Hotta N. Two-week continuous supplementation of hydrogenrich water increases peak oxygen uptake during an incremental cycling exercise test in healthy humans: a randomized, single-blinded, placebo-controlled study. *Medical Gas Research*. 2020;10(4):163-9.
10.4103/2045-9912.304223
19. LeBaron TW, Laher I, Kura B, Slezak J. Hydrogen gas: from clinical medicine to an emerging ergogenic molecule for sports athletes. *Canadian Journal of Physiology and Pharmacology*. 2019;97(9):797-807.
10.1139/cjpp-2019-0067
20. Su Z, Liu Y, Zhang H. Adaptive Cardiac Metabolism Under Chronic Hypoxia: Mechanism and Clinical Implications. *Frontiers in Cell and Developmental Biology*. 2021;9(91).
10.3389/fcell.2021.625524
21. Dedukhova VI, Loginova EV, Malkin VB, Mokhova EN, Roshchina NA. [Mechanism of adaptation to hypoxic hypoxia]. *Kosmicheskaja biologija i meditsina*. 1972;6(4):9-14.
22. Essop MF. Cardiac metabolic adaptations in response to chronic hypoxia. *J Physiol*. 2007;584(Pt 3):715-26. *10.1113/jphysiol.2007.143511*
23. Niu Y, Nie Q, Dong L, Zhang J, Liu SF, Song W, et al. Hydrogen Attenuates Allergic Inflammation by Reversing Energy Metabolic Pathway Switch. *Scientific reports*. 2020;10(1):1962-. *10.1038/s41598-020-58999-0*
24. LeBaron TW, Singh RB, Fatima G, Kartikey K, Sharma JP, Ostojic SM, et al. The Effects of 24-Week, High-Concentration Hydrogen-Rich Water on Body Composition, Blood Lipid Profiles and Inflammation Biomarkers in Men and Women with Metabolic Syndrome: A Randomized Controlled Trial. *Diabetes Metab Syndr Obes*. 2020;13:889-96. *10.2147/DMSO.S240122*
25. LeBaron TW, Larson AJ, Ohta S, Mikami T, Barlow J, Bulloch J, et al. Acute Supplementation with Molecular Hydrogen Benefits Submaximal Exercise Indices. Randomized, Double-Blinded, Placebo-Controlled Crossover Pilot Study. *J Lifestyle Med*. 2019;9(1):36-43. *10.15280/jlm.2019.9.1.36*
26. Botek M, Sládečková B, Krejčí J, Pluháček F, Najmanová E. Acute hydrogen-rich water ingestion stimulates cardiac autonomic activity in healthy females. *Acta Gymnica*. 2021;51(1).
10.5507/ag.2021.009
27. Zálešák M, Kura B, Graban J, Farkašová V, Slezák J, Ravingerová T. Molecular hydrogen potentiates beneficial anti-infarct effect of hypoxic postconditioning in isolated rat hearts: a novel cardioprotective intervention. *Can J Physiol Pharmacol*. 2017;95(8):888-93. *10.1139/cjpp-2016-0693*
28. LeBaron TW, Kura B, Kalocayova B, Tribulova N, Slezak J. A New Approach for the Prevention and Treatment of Cardiovascular Disorders. Molecular Hydrogen Significantly Reduces the Effects of Oxidative Stress. *Molecules*. 2019;24(11):2076.
10.3390/molecules24112076
29. Guan P, Sun Z-M, Luo L-F, Zhao Y-S, Yang S-C, Yu F-Y, et al. Hydrogen Gas Alleviates Chronic Intermittent Hypoxia-Induced Renal Injury through Reducing Iron Overload. *Molecules*. 2019;24(6):1184.
10.3390/molecules24061184
30. Zhao Y-S, An J-R, Yang S, Guan P, Yu F-Y, Li W, et al. Hydrogen and Oxygen Mixture to Improve Cardiac Dysfunction and Myocardial Pathological Changes Induced by Intermittent Hypoxia in Rats. *Oxid Med Cell Longev*. 2019;2019:7415212-.
10.1155/2019/7415212

31. Guan P, Lin X-M, Yang S-C, Guo Y-J, Li W-Y, Zhao Y-S, et al. Hydrogen gas reduces chronic intermittent hypoxia-induced hypertension by inhibiting sympathetic nerve activity and increasing vasodilator responses via the antioxidation. *Journal of Cellular Biochemistry*. 2019;120(3):3998-4008.
<https://doi.org/10.1002/jcb.27684>
32. Hayashi T, Yoshioka T, Hasegawa K, Miyamura M, Mori T, Ukimura A, et al. Inhalation of hydrogen gas attenuates left ventricular remodeling induced by intermittent hypoxia in mice. *American Journal of Physiology-Heart and Circulatory Physiology*. 2011;301(3):H1062-H9. [10.1152/ajpheart.00150.2011](https://doi.org/10.1152/ajpheart.00150.2011)
33. Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One*. 2020;15(11):e0240784-e.
[10.1371/journal.pone.0240784](https://doi.org/10.1371/journal.pone.0240784)
34. Zanini D, Stajer V, Ostojic SM. Hydrogen vs. Caffeine for Improved Alertness in Sleep-Deprived Humans. *Neurophysiology*. 2020;52(1):67-72.
[10.1007/s11062-020-09852-7](https://doi.org/10.1007/s11062-020-09852-7)
35. Todorovic N, Zanini D, Stajer V, Korovljev D, Ostojic J, Ostojic SM. Hydrogen-rich water and caffeine for alertness and brain metabolism in sleep-deprived habitual coffee drinkers. *Food Science & Nutrition*.00:1-7.
<https://doi.org/10.1002/fsn3.2480>
36. Lucas K, Rosch M, Langguth P. Molecular hydrogen (H₂) as a potential treatment for acute and chronic fatigue. *Archiv der Pharmazie*. 2021;354(4):2000378.
<https://doi.org/10.1002/ardp.202000378>
37. LeBaron TW, Asgharzadeh F, Khazei M, Kura B, Tarnava A, Slezak J. Molecular hydrogen is comparable to sulfasalazine as a treatment for DSS-induced colitis in mice. *EXCLI J*. 2021;20:1106-17.
[10.17179/excli2021-3762](https://doi.org/10.17179/excli2021-3762)
38. Runtuwene J, Amitani H, Amitani M, Asakawa A, Cheng K-C, Inui A. Hydrogen-water enhances 5-fluorouracil-induced inhibition of colon cancer. *PeerJ*. 2015;3:e859-e.
[10.7717/peerj.859](https://doi.org/10.7717/peerj.859)
39. Jiang Z, Alamuri TT, Muir ER, Choi DW, Duong TQ. Longitudinal multiparametric MRI study of hydrogen-enriched water with minocycline combination therapy in experimental ischemic stroke in rats. *Brain Research*. 2020;1748:147122.
<https://doi.org/10.1016/j.brainres.2020.147122>
40. Hong C-T, Hu C-J, Lin H-Y, Wu D. Effects of concomitant use of hydrogen water and photobiomodulation on Parkinson disease: A pilot study. *Medicine (Baltimore)*. 2021;100(4):e24191-e.
[10.1097/MD.00000000000024191](https://doi.org/10.1097/MD.00000000000024191)