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Hydrogen Inhalation Therapy Saves Lives and Improves Outcomes for Out-of-Hospital Cardiac Arrest Patients

A study conducted across 15 emergency medical facilities in Japan has shown that hydrogen gas (H₂) inhalation increased the possibility of neurologically intact survival among patients who remain comatose following the return of spontaneous circulation from out-of-hospital cardiac arrest (OHCA). The multicenter, double-blind, randomized controlled trial¹ was conducted as part of the activities of the Keio University Center for Molecular Hydrogen Medicine and was led by Professor Masaru Suzuki of the Tokyo Dental College (Specially Appointed Professor at Keio University Global Research Institute) and assistant professors Koichiro Honma (Emergency Medicine) and Motoaki Sano (Cardiology) of the Keio University School of Medicine, among others.

When a victim suffers sudden cardiogenic cardiac arrest, immediate cardiopulmonary resuscitation is crucial in restoring their circulation and saving their life. In those who initially restore spontaneous circulation after OHCA, the significant subsequent morbidity and mortality are primarily due to the cerebral and cardiac dysfunction that accompanies prolonged whole-body ischemia. This state, called post-cardiac arrest syndrome, comprises anoxic brain injury, post-cardiac arrest myocardial dysfunction, systemic ischemia/reperfusion response, and persistent precipitating pathology. With the brain's heightened susceptibility to global ischemia, the majority of cardiac arrest patients who are successfully resuscitated have impaired consciousness, and some remain in a vegetative state. No effective therapy that diminishes the ischemia/reperfusion injury has been developed yet besides targeted temperature management², which is recommended by international guidelines.

This research group previously reported that inhalation of H₂ after cardiac arrest reduces mortality and brain injury in a rodent model. However, there has been no evidence in human clinical settings. To determine whether the H₂ inhalation therapy improved neurologically intact patients who remain comatose following the return of spontaneous circulation from OHCA, the group conducted a multicenter, double-blind, randomized controlled trial, the most reliable trial method at emergency medical facilities in Japan.

As the study was terminated prematurely because the COVID-19 pandemic led to a drastic increase in the demand for ventilators and a chronic staff shortage that hampered patient

enrollment, the increase in participants with good neurological outcomes following post-OHCA H₂ inhalation in a selected population of patients was not statistically significant.

However, the secondary outcomes suggest that H₂ inhalation may increase 90-day survival from 61% to 85%. Further, 90-day survival with no neurological deficits increased from 21% to 46%.

H₂ has been recognized as safe for the human body, and no side effects attributable to H₂ were observed in this clinical trial. This treatment is expected to save the lives of many patients when implemented in clinical settings.

The results of this study were published in *eClinicalMedicine* on March 17, 2023 (JST).

1. Background and Overview of This Study

OHCA is a common first symptom of cardiovascular disease, affecting 100,000 people in Japan each year. Of these, approximately 60,000 people suffered from heart disease (cardiogenic cardiac arrest), with the one-month survival rate reaching up to 8%. Even if patients initially achieve the return of spontaneous circulation, the significant subsequent morbidity and mortality are primarily due to cerebral dysfunction, and more than half will be severely disabled.

Cardiac arrest causes severe ischemic insult on whole-body organs. Once spontaneous circulation is established during basic or advanced life support, the supply of blood and oxygen is restored to ischemic organs, leading to reperfusion injury (called post-cardiac arrest syndrome). With the brain's heightened susceptibility to global ischemia, the majority of cardiac arrest patients who are successfully resuscitated have impaired consciousness, and some remain in a vegetative state. The only standard treatment to relieve such post-cardiac arrest syndrome is targeted temperature management. Although it has been recommended by international guidelines, its effectiveness is not established.

The research group found that H₂ is as effective as temperature management therapy in mouse models of cardiac arrest and that the greatest cerebral protective effect is achieved through a combination of H₂ inhalation and temperature management therapy (Reference 1). In a previous first-in-human pilot study, 5 patients were treated with H₂ inhalation, and 4 (80%) experienced full neurological recovery (Reference 2).

Therefore, the group conducted this clinical trial to clarify the effects of H₂ inhalation on OHCA patients with post-cardiac arrest using the most reliable method, a double-blind, randomized controlled trial, with the cooperation of emergency medical facilities throughout Japan.

2. Results and Significance of This Study

Patients with cardiogenic OHCA who regained spontaneous circulation but remained comatose were included in this trial. They were admitted to the ICU and underwent standard targeted temperature management, with one group (the H₂ group) inhaling 2% hydrogenated oxygen for 18 hours while the other group (the control group) received no H₂ (See Fig. 1). Their 90-day neurological outcomes were evaluated by two independent neurologists. A total of 73 patients were eligible for the study (39 in the H₂ group and 34 in the control group). Unfortunately, the study had to be terminated due to COVID-19, which caused a strain on emergency medical care. Therefore, it was inconclusive as to whether the H₂ inhalation therapy was effective. Nevertheless, the fully intact survival rate after 90 days increased from 21% in the control group to 46% in the H₂ group, and the survival rate increased from 61% to 85%. These differences were statistically significant, and no apparent side effects were associated with H₂ inhalation in this clinical trial.

In the future, H₂ inhalation therapy is expected to become a breakthrough treatment for patients suffering from post-cardiac arrest syndrome, helping them regain consciousness and preventing neurological aftereffects.

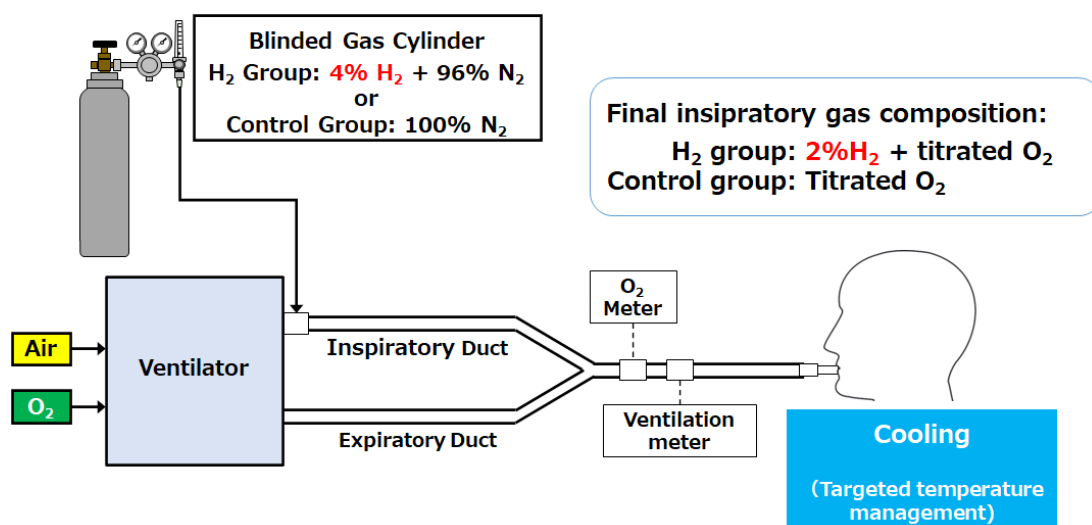


Fig. 1 Hydrogen gas inhalation system

3. Special Notes

This study was supported by Taiyo Nippon Sanso Co. The title of the study was "Efficacy of inhaled HYdrogen on neurological outcome following BRain Ischemia During post-cardiac arrest care (Phase II, multicenter, prospective, randomized, double-blinded, placebo-controlled trial)" (clinical research protocol numbers: jRCTs031180352, UMIN000019820), and the facilities where the cases were enrolled were as follows: Keio University Hospital, Kyoto Second Red Cross Hospital, Yamaguchi University Hospital, Fujisawa Municipal Hospital, Kagoshima University Hospital, Mie University Hospital, Yamaguchi Prefectural General Medical Center, Tokuyama Central Hospital, Kagoshima City Hospital, Hiroshima University Hospital, Kagawa University Hospital, National Hospital Organization Kumamoto Medical Center, Kawasaki City Hospital, Kawasaki City Hospital, National International Medical Center Hospital, Kawasaki City Hospital, National Center for Global Health and Medicine Hospital, and Juntendo University Shizuoka Hospital.

4. Research Paper

Title: *Efficacy of inhaled HYdrogen on neurological outcome following BRain Ischaemia During post-cardiac arrest care (HYBRID II): study protocol for a randomized controlled trial*

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2. T Tamura et al. "Feasibility and Safety of Hydrogen Gas Inhalation for Post-Cardiac Arrest Syndrome - First-in-Human Pilot Study." *Circulation Journal*. *Circ J* 2016;80:1870-3. doi: 10.1253/circj.CJ-16-0127.

Glossary

¹ Multicenter, double-blind, randomized controlled trial

A type of study design in which all parties involved in conducting the clinical trial are completely unaware of what drug is being administered. It is the most common method used in comparative studies for confirming the therapeutic efficacy and effectiveness of new drugs (test drugs). Subjects are divided into two groups, with one group receiving the test drug and the other group receiving a control drug (e.g., placebo), with physicians, patients, and staff members unaware of which group is receiving which drug. The results of each group are then compared and evaluated to determine if the test drug is effective.

² Targeted temperature management

Targeted temperature management is a treatment method that includes "therapeutic hypothermia" and "anti-hyperthermia / induced normothermia" and aims to protect the central nervous system and prevent the progression of brain damage by avoiding hyperthermia.

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