



Feasibility and Safety of Hydrogen Gas Inhalation for Post-Cardiac Arrest Syndrome

– First-in-Human Pilot Study –

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Background: Hydrogen gas inhalation (HI) ameliorates cerebral and cardiac dysfunction in animal models of post-cardiac arrest syndrome (PCAS). HI for human patients with PCAS has never been studied.

Methods and Results: Between January 2014 and January 2015, 21 of 107 patients with out-of-hospital cardiac arrest achieved spontaneous return of circulation. After excluding 16 patients with specific criteria, 5 patients underwent HI together with target temperature management (TTM). No undesirable effects attributable to HI were observed and 4 patients survived 90 days with a favorable neurological outcome.

Conclusions: HI in combination with TTM is a feasible therapy for patients with PCAS. (*Circ J* 2016; **80**: 1870–1873)

Key Words: Hydrogen gas inhalation; Molecular hydrogen; Post-cardiac arrest syndrome; Return of spontaneous circulation

Anoxious neurological injury is a significant source of morbidity and mortality in patients with post-cardiac arrest syndrome (PCAS). Although a growing body of evidence suggests that target temperature management (TTM) is important for improving neurological outcomes,¹ TTM requires significant human and material resources and can only be performed by experienced teams in the intensive care unit (ICU).² We have been looking for widely applicable therapeutic approaches for PCAS. Recent proof-of-concept studies in animal models have demonstrated the therapeutic effect of molecular hydrogen (H₂) on neurological outcomes after cardiac arrest (CA).^{3,4} In this study, we sought to evaluate the feasibility and safety of H₂ inhalation (HI) for PCAS.

Methods and Results

The study was an open-label, single-arm, prospective intervention trial performed at Keio University Hospital in Tokyo, Japan. The study protocol was approved by the Ethics Committee of Keio University. We consecutively enrolled 5 patients who met the inclusion/exclusion criteria between January 1, 2014, and January 19, 2015 (**Figures A,B**): 3 of the

patients (60%) were male, and the average age was 65±15 years. Collapse was witnessed for all patients; 4 patients (80%) had received bystander-performed cardiopulmonary resuscitation, 4 patients (80%) were initially in ventricular fibrillation, and 4 patients (80%) had a cardiac etiology. The time interval from collapse until return of spontaneous circulation (ROSC) was 16±4.7 min, and the time from ROSC until the initiation of HI was 4.9±1.2 h (**Table**). Written informed consent was obtained from a legal surrogate and from each patient who regained the necessary mental capacity. Comprehensive PCAS care was provided according to guidelines.⁵ All patients were successfully treated with TTM between 33°C and 36°C.

HI (2% H₂ with oxygen) was initiated through a ventilator upon ICU admission and was continued for 18 h. During HI, patients were ventilated using volume-controlled continuous mandatory ventilation in combination with sedatives and neuromuscular blocking agents. The actual respiratory conditions, tidal volume, FiO₂, end-tidal CO₂, and H₂ concentration was continuously monitored by additionally installed monitoring devices (**Figures C,D**). HI was successfully applied to all the eligible patients as scheduled.

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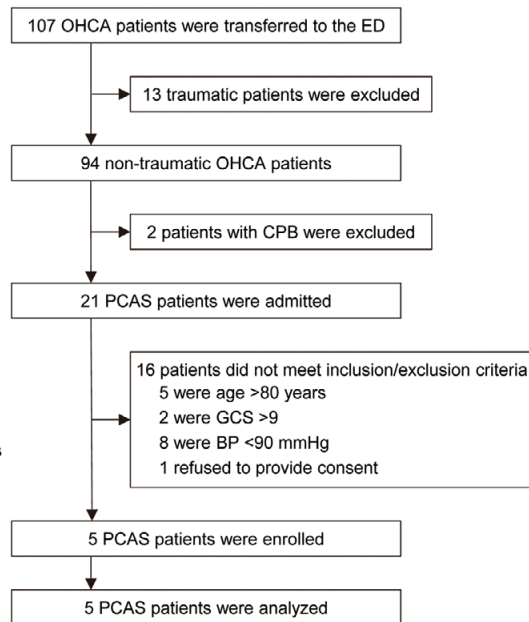
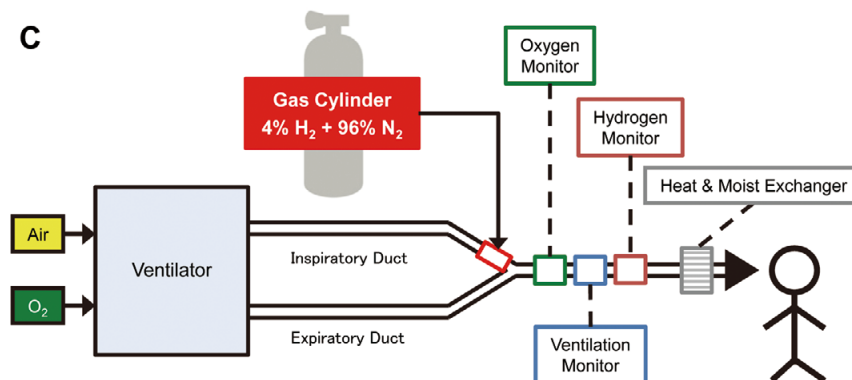
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A**Inclusion criteria**

1. Achieved ROSC irrespective of the initial cardiac rhythm after an OHCA.
2. An age between 20 and 80 years.
3. Sustained coma (GCS \leq 8) upon admission.

Exclusion criteria

1. Traumatic cardiac arrest.
2. Acute aortic dissection.
3. Known pre-arrest CPC of 3 or 4.
4. Known limitations in therapy and a "do not resuscitate" order.
5. Oxygen saturation of <95% with 50% oxygen inhalation and adequate positive end-expiratory pressure.
6. Systolic blood pressure <90 mmHg despite adequate fluids and vasopressors and/or inotropes support.
7. Elapse of more than 12 h after ROSC prior to the initiation of HI.
8. Pregnancy.

B**C****D**

Targeted goals of respiratory condition			Ventilator Setting			Hydrogen Gas Cylinder
Tidal Volume (mL)	Respiratory Rate (/min)	FiO ₂	Tidal Volume (mL)	Respiratory Rate (/min)	FiO ₂	Flow Rate (L/min)
500	10	0.5	250	10	1.0	6.3
		0.4			0.8	
	12	0.5		12	1.0	7.5
		0.4			0.8	
	15	0.5		15	1.0	9.4
		0.4			0.8	
400	10	0.5	200	10	1.0	5.0
		0.4			0.8	
	12	0.5		12	1.0	6.0
		0.4			0.8	
	15	0.5		15	1.0	7.5
		0.4			0.8	

Figure. Patient selection and system of HI therapy. **(A)** Inclusion and exclusion criteria. **(B)** Flow diagram of the patient selection process. **(C)** Regulated oxygen from the ventilator was mixed with gas from a cylinder filled with 4% H₂ and 96% N₂ at the end of the inspiratory duct. To ensure safety, we installed the monitoring devices (oxygen, ventilation, and hydrogen concentration monitor) in the respiratory circuit for inspection of the actual composition of the mixed gas during the administration. **(D)** To administer 2% H₂ while maintaining normoxia (avoiding hyperoxia) and normocapnia in patients, we measured the composition of the mixed gas and predetermined the flow rate of the gas from the cylinder in 12 different combinations with a designated tidal volume, respiratory rate, and FiO₂. CPB, cardiopulmonary bypass; CPC, cerebral performance category; FiO₂, fraction of inspiratory oxygen; GCS, Glasgow Coma Scale; HI, hydrogen gas inhalation; OHCA, out-of-hospital cardiac arrest; PCAS, post-cardiac arrest syndrome; ROSC, return of spontaneous circulation.

Table. Post-Cardiac Arrest Syndrome Patients Clinical Characteristics and Outcomes

	Patient no.				
	1	2	3	4	5
Age (years)	65	77	46	80	54
Sex	F	M	M	F	M
Witness status	Yes	Yes	Yes	Yes	Yes
Bystander-performed CPR	Yes	Yes	Yes	No	Yes
First monitored rhythm	Asystole	VF	VF	VF	VF
Presumed cardiac arrest time (min)	25	15	16	14	24
Diagnosis	Pneumonia	Hyperkalemia	AMI	HOCM	AMI
GCS before HI	3	3	7	6	6
Emergency CAG	No	Yes	Yes	No	Yes
Emergency PCI	No	No	Yes	No	Yes
Time from ROSC to HI (h)	3.7	7	5.4	4.9	3.8
Target temperature (°C)	36	34	34	34	34
Time from ROSC to target temperature (h)	0.5	10.0	8.8	7.0	5.8
AEs attributable to HI	None	None	None	None	None
NSE (ng/ml)	NA	36.2	12.8	22.6	64.8
90-day survival	No	Yes	Yes	Yes	Yes
90-day CPC	5	1	1	1	1

AE, adverse event; AMI, acute myocardial infarction; CAG, coronary angiography; CPR, cardiopulmonary resuscitation; GCS, Glasgow Coma Score; HI, hydrogen gas inhalation; HOCM, hypertrophic obstructive cardiomyopathy; NSE, neuron-specific enolase; PCI, percutaneous coronary intervention; ROSC, return of spontaneous circulation; VF, ventricular fibrillation.

Predefined adverse events (AEs) were recorded daily until 7 days after CA, including cardiac re-arrest, atrial arrhythmia, ventricular arrhythmia, atrioventricular block, sick sinus syndrome, acute coronary syndrome, pericardial effusion, cardiac tamponade, in-stent restenosis, high blood pressure, low blood pressure, thromboembolism, vasculitis (arteritis/phlebitis), acute respiratory distress syndrome, ventilator-associated pneumonia, pneumonia, bronchitis, hypoxia, aspiration pneumonia, atelectasis, pleural effusion, intrathoracic hemorrhage, tracheal stenosis, gastrointestinal bleeding, ileus, ulcer, visceral arterial ischemia, ischemic colitis, diarrhea, liver failure, cholecystitis, cholangitis, pancreatitis, acute renal failure, chronic renal failure, pyelonephritis, cystitis, hematuria, loss of brainstem reflex, cerebral vascular disorder, seizure, myoclonus, limb paralysis, Stevens-Johnson syndrome, urticaria, edema, sepsis, septic shock, surgical site infection, catheter-related blood stream infection, anaphylaxis, falls, fractures, contusions, complications associated with the surgical procedure, and blood test values outside of the institutional reference ranges (Table S1). The Data and Safety Monitoring Committee reviewed all AEs and examined their causal relationships with events and HI, concluding that no AEs were causally related to HI.

The neurological intact survival rates (ie, patients with cerebral performance category (CPC) of 1–2) were assessed at 90 days after CA. An outcome of CPC 1 had been achieved by 4 of the 5 patients. One CA patient with severe pneumonia and septic shock died of respiratory deterioration 22h after the discontinuation of HI.

Discussion

To the best of our knowledge, this was a first-in-human study to evaluate the feasibility and safety of HI during PCAS care. HI did not interfere with PCAS care, including TTM. Although most AEs are of a potentially serious nature, they are often common in PCAS patients with or without HI. No AEs related

to HI were observed. We concluded that HI is a safe and feasible procedure for patients with PCAS and thus can be considered as a novel therapeutic approach for PCAS patients.

We sought to establish a safe method to administer titrated H₂ gas through a ventilator. First, we chose a premixed gas of 4% H₂ and 96% nitrogen (N₂) to be mixed with oxygen so that the H₂ gas concentration did not exceed an explosive threshold of 4% at room temperature. Second, we chose a specific kind of ventilator that uses an ultrasonic flow sensor (SERVO-i®; MAQUET Critical Care AB, Sweden) as the flow meters. Most of the available ventilators today are equipped with platinum hot-wire anemometers, which could overheat and ignite when the H₂ is mixed. Thus the selection of the ventilator is particularly important. Third, to safely achieve the target of respiration, we had examined this H₂ administration ventilator system and predetermined the patterns for the ventilator settings during the preclinical phase.

We recognize several limitations. First, because the aim of study was to evaluate the feasibility and safety of the clinical translation of HI, the patients were highly selected. Second, the sample size was small, and further larger studies are required to confirm these results. However, it is well worth noting that the survival rate and the percentage of CPC 1 were 100% among the patients with a cardiac etiology, and even the PCAS patient with high neuron-specific enolase levels, which is a strong predictor of poor neurological outcome after OHCA, achieved a favorable neurological outcome after HI. Third, the duration of HI was restricted to 18 h because of the capacity of the gas cylinder. From our experience in patients with septic shock, prolonged HI may be desirable.

Conclusions

HI in combination with TTM is a safe and feasible therapeutic approach for patients with PCAS. We are planning a larger, phase 2 clinical study to evaluate the safety and efficacy of HI for patients with PCAS (UMIN: 000019820).

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Supplementary Files

Supplementary File 1

Table S1. Institutional reference ranges for laboratory test results

Please find supplementary file(s);
<http://dx.doi.org/10.1253/circj.CJ-16-0127>