



Preliminary experimental outcomes of induced hypercapnia in treatment of obstinate singultus

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Background: Our team found that abolishing the venous-arterial CO₂ gradient can cease singultus (hiccups), in which the CO₂ pressure in blood reaches no less than 50 mmHg. In order to precisely investigate the target level as a preliminary study, we made a combination gas consisting of 10% CO₂ and 90% O₂ to generate the conditions instantly and safely.

Methods: Thirty-five cases consisting of 26 patients with long-term chronic singultus were treated using the gas. The group consisted of 21 males and 5 females with mean singultus duration of 8.0±13.1 years. A standard oxygen mask was used for delivery of the gas to the patients, and patients breathed in the gas until they felt relief. The duration of the procedure was measured from the beginning to the point at which singultus ceased. A blood test was performed to measure the partial pressure of CO₂ in venous blood at the point at which singultus ceased.

Results: Singultus ceased in all patients in a mean time of 5.3±1.5 minutes, with complete recurrence observed in two cases. The mean partial pressure of CO₂ in the venous blood at the point the singultus stopped was 60.8±6.8 mmHg. No life-threatening complications were found in any patient.

Conclusions: One of the definitive conditions for ceasing singultus is acute CO₂ retention in the body, the target of which is around 60 mmHg of CO₂ in venous blood. We believe that targeting acute hypercapnia can always stop singultus, although further neuroscientific investigation is necessary to reveal the physiological mechanism.

Keywords: Hiccups; carbon-dioxide; hypercapnia

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Introduction

Our team discovered that subjecting the body to acute hypercapnia creates the physiological conditions necessary to stop singultus, or hiccups (1,2). The partial pressure of CO₂ in arterial blood must reach no less than 50mmHg and the CO₂ pressure gradient between arterial and venous blood must disappear almost completely to be effective (1,2). In order to investigate these conditions precisely, we had a

combination gas consisting of 10% CO₂ and 90% O₂ made for patients to inhale, aiming to create the above conditions instantly and safely; we thought that if patients continued breathing in the gas, their CO₂ pressure in blood should constantly increase from normal level to about 70 mmHg within a few minutes. If the gas successfully ceased their hiccups, the precise target to stop them would be revealed. Incidentally, according to our former report, a CO₂ pressure gradient between venous-arterial blood should be

found until CO₂ pressure in arterial blood is below around 50 mmHg, and after that point the pressure gradient should be abolished (1,2). We report the preliminary experimental outcomes of treatment for chronic singultus using induced hypercapnia and discuss the next step forward regarding treatment. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/jtd-20-1049>).

Methods

The study protocol was examined and approved by our institutional review board (Institutional Review Board of St. Mary's Hospital; No. 16-1010 and No. 19-0606, approved on Oct. 31, 2016 and Jun. 30, 2019, respectively). Clinical trial No. was UMIN000037704 and registered on August 17, 2019. This study was registered as UMIN000037704 on August 17, 2019 and was conducted in accordance with the Helsinki Declaration (as revised in 2013).

Participants

From August 2019 to March 2020, a total of 26 patients with long-term intractable singultus were treated with the combination gas at our institution. All patients agreed to participate in our study to stop singultus using the gas, and written informed consent was obtained from the participants. The group consisted of 21 males and 5 females with a mean age of 70.0±12.8 years (*Table 1*), and the mean duration of hiccups was 8.0±13.1 years, with a range of 5 days to 66 years. All patients had undergone numerous treatments, both home remedies and standard medications (such as injection of metoclopramide), with no lasting effect. It is worth noting that all patients who requested treatment at our institution during this time were included in the study and are presented in consecutive order in the data tables.

Materials

The combination gas consisting of 10% CO₂ and 90% O₂ was ordered through a gas company (Kyushu Air Water) in Kumamoto Prefecture, Japan. A standard oxygen mask was used for delivery of the combination gas to the patient, whose head was completely covered with a 45 L (650×800 mm²) clear plastic bag (*Figure 1*). An airtight seal was made around the neck using plastic tape in order to prevent the gas from escaping into the atmosphere and

reducing the effectiveness of the procedure. To prevent the plastic bag from clinging to the nostrils or mouth, patients wore a baseball cap or a hat with a wide brim.

Procedure

After the oxygen mask, hat, and plastic bag were fully in place, we administered the combination gas to each patient at a rate of 2–6 L/min, paying attention to overpressure inside the bag. Patients were instructed to continue breathing normally inside the bag until they felt their singultus stop. A pulse oximeter was used to continuously monitor the peripheral capillary oxygen saturation (SpO₂) and heart rate (HR) of the patients, for their safety.

The duration of the procedure was measured from the beginning to the point at which singultus ceased. If patients agreed, a blood test was performed to measure the partial pressure of CO₂ in venous blood at the point at which singultus ceased, and also before the procedure. Incidentally, according to our previous study, we regarded CO₂ pressure in arterial blood as almost the same value as that in venous blood when they were over 50 mmHg (2).

Results

A total of 35 cases consisting of 26 consecutive patients with persistent or intractable singultus were treated with the combination gas. The group consisted of 21 males and 5 females, and the mean duration of singultus was 8.0±13.1 years (mean ± SD). We administered the combination gas to each patient. Singultus was successfully stopped in all patients in a mean time of 5.3±1.5 minutes. In 13 of the 35 cases, recurrence occurred while in the clinic, and the same procedures were re-performed; the second treatments were also effective in those cases. In patient No.2 and No.34, however, singultus restarted a few minutes after the procedure again and again. Patient No.2 agreed to 4 subsequent attempts, and patient No.34 did 2 attempts, but none resulted in long-term relief in both patients. Life-threatening complications were not found in any patient.

The blood test was performed in 23 cases (consisting of 20 patients) of the 35 cases; the mean partial pressure of CO₂ in the venous blood at the point the singultus stopped was 60.8±6.8 mmHg, whereas that before the procedure was 46.8±6.7 mmHg. The mean HR at the beginning of the procedure was 75.9±13.0 bpm and at the time hiccups stopped was 89.3±14.9 bpm (17.7% increase). Incidentally, all data was collected at the first trial of each case.

Table 1 Patient characteristics and results

Patient No.	Age (years)	Sex	Duration of hiccups continuing (years)	Comorbidity	Duration of procedure (min)	SpO ₂ (%)	Recurrence while in clinic
1	45	F	2	Depression	5.6	99	No
2	81	M	18	None	6.0	100	Yes
3	49	M	10	Mental retardation	3.0	100	No
4	82	F	66	None	1.9	100	No
5	70	M	13	None	8.0	100	No
6 ^A	69	M	2.5	OMI, CHF, PM	5.1	100	No
7	79	M	6	CRF, DM	5.0	100	No
8	49	F	8 months	None	5.0	100	Yes
9	52	M	7 days	HD	6.5	100	Yes
10	73	M	4.5	CRF, DM, Aplastic anemia	7.0	100	Yes
11	84	F	4	DM, Epilepsy	6.0	100	No
12	61	M	2	HD, Thalamic hemorrhage	5.0	100	Yes
13	70	M	5	Cereb infarc, tSAH	6.0	100	No
14	77	M	7	GERD, Cereb infarc	5.0	100	Yes
15 ^A	69	M	2.5	See No. 6	6.0	100	Yes
16	76	M	5 days	None	4.5	100	No
17	57	M	4.5	Mental retardation	9.0	100	Yes
18 ^B	88	M	10	Asthma	7.0	100	No
19	56	M	9 days	Herpes pharyngitis	5.7	100	Yes
20 ^B	88	M	10	See No. 18	5.6	100	No
21 ^C	84	M	4 months	VCF of Th11	5.8	100	No
22	56	M	6	DM	5.1	100	Yes
23 ^A	69	M	3	See No. 6	6.0	100	No
24	79	M	10 days	Asthma	6.0	99	No
25 ^D	81	M	8	VCF of Th11	3.0	100	No
26	68	M	3	Cholecystectomy	7.5	100	No
27 ^E	79	M	20	DM, GERD	5.0	100	No
28 ^F	82	M	16	DM, COPD	4.0	100	No
29 ^E	79	M	20	See No. 27	3.0	100	No
30 ^D	81	M	8	See No. 25	6.1	100	No
31 ^B	89	M	10	See No. 18	4.0	100	No
32 ^F	82	M	16	See No. 28	4.0	100	No
33 ^C	84	M	4 months	See No. 21	4.0	99	Yes
34	73	F	2 months	Dementia	5.0	100	Yes
35 ^C	84	M	4 months	See No. 21	5.0	99	Yes

Numbers 6, 15 and 23 (patient^A), numbers 18, 20 and 31 (patient^B), numbers 21, 33 and 35 (patient^C), numbers 25 and 30 (patient^D), numbers 27 and 29 (patient^E), and numbers 28 and 32 (patient^F) are the same patients, respectively. Cereb infarc, cerebral infarction; CHF, chronic heart failure; CRF, chronic renal failure; DM, diabetes mellitus; GERD, gastroesophageal reflux disease; HD, hemodialysis; OMI, old myocardial infarction; PM, pacemaker; SpO₂, peripheral capillary oxygen saturation; tSAH, traumatic subarachnoid hemorrhage; VCF, vertebral compression fracture.



Figure 1 Combination gas is delivered through the oxygen mask. A plastic bag is necessary to prevent CO₂ from escaping into the atmosphere, and the hat prevents the plastic bag from clinging to the nostrils or mouth (the model is not the patient but a staff member).

Discussion

Singultuses are involuntary movements triggered from afferent signals such as through the glossopharyngeal nerve, vagus nerve, phrenic nerve and sympathetic nerves (T6–T12), and involve rapid inspiration and sudden closing of both the vocal cords and epiglottis (3-6). Since the movements are related to the innervation areas of the phrenic nerves and vagus nerve, it is presumed that the “hiccup epicenter” is located near the nucleus tractus solitarius in the medulla (1-3). Sudden contraction of the diaphragm generates strong negative pressure in the air tract, and air aspirated through the narrow space between the vocal cords as they slam shut creates the high-pitch ‘hic’ noise we know as a hiccup (3,4).

Although the nature of singultus is still a mystery (3,4), it has been believed since ancient times that CO₂ retention in the body should lead singultus to stop (7). In fact, many researchers have studied about it using paper-bag rebreathing and CO₂ inhalation; CO₂ affects the central nervous system (CNS) and ceases singultus, although the precise mechanism has not been completely revealed as of yet (5-8). According to historical evidence, it is thought that CO₂ has some potential to cut the circuit of singultus in the CNS (7,8). On this ground, treatment using CO₂ would possibly be a radical therapy for singultus (7). Unfortunately, however, methods such as paper-bag rebreathing are still considered to be home remedies, even now (4,6). Probably because of their unstable reproducibility, it may well be difficult for many physicians to take them seriously as a

standard therapy (8).

As mentioned in our previous report (1), our team thought that the unstable reproducibility of CO₂ retention methods was probably caused by an insufficient level of CO₂ in the body, especially in the CNS. According to Petroianu, modest concentration of CO₂ in the body can explain the limited success of paper-bag rebreathing therapies for singultus (8). For CO₂ concentrations in patients to be a reliable treatment option, PaCO₂ should increase, for example from 40 to 50 mmHg, so as to sufficiently decrease the pH in the CNS to suppress excitability of the respiratory center (8). From this point of view, our method increased PaCO₂ so steadily from 40 to around 70 mmHg that excitability of the CNS was able to be sufficiently suppressed to cease persistent or intractable singultus in all of our patients. In our previous reports, singultus stopped in hypercapnia when the venous-arterial CO₂ gradient was abolished; it occurred when PaCO₂ reached no less than 50 mmHg. The present study more precisely revealed that it occurs around 60 mmHg, even though the precise point was different in each patient. In theory, our method can always reach and pass the threshold point, which is between about 50 and 76 mmHg. That is the reason for being able to successfully calm CNS excitability in order to cease singultus.

Although our team has some speculations about possible mechanisms, one of which is activation of fight-or-flight response (9), the actual mechanism of how CO₂ retention can terminate singultus effectively using our method is still a difficult question. Further investigation and cooperation with other researchers are necessary to reveal this mystery completely.

Nonetheless, our team found several interesting facts through this experimental treatment. Firstly, our team can provide mental relief for patients because many of them believed that their singultus would never cease by such treatments. Despite the fact that the effect did not always last for a long period, they realized that there is at least one reliable method to instantly stop singultus at their will. In fact, a few patients with intractable singultus returned to the hospital to stop it again from time to time when they were annoyed by the recurrence. We are confident that the certainty and reliability of our treatment can often relieve patients’ psychological burden. Secondly, we have realized that the restarting mechanism is the actual mystery of singultus. We thought that singultus problems would be resolved for good if only we could simply stop the hiccups. Actually, however, hiccups often recurred in patients

with chronic singultus, in the same way that arrhythmia sometimes recurs after being successfully terminated using a defibrillator. It is crucial to find the “ignition” that restarts the singultus circuit. Lastly, other researchers can easily conduct conformation experiments, as our results demonstrated that the threshold to stop singultus was around 60 mmHg of PaCO₂ as well as PvCO₂. To the best of our knowledge, there was no report with even 26 patients with persistent or intractable singultus, and where singultus was successfully stopped in all cases, even only temporarily. We believe that this number demonstrates that our method is highly promising. It is our sincere hope that many researchers will join this field and refine our method and theory.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/jtd-20-1049>

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was examined and approved by our institutional review board (Institutional Review Board of St. Mary's Hospital; No. 16-1010 and No. 19-0606, approved on Oct. 31, 2016 and June 30, 2019, respectively). Clinical trial No. was UMIN000037704 and registered on August 17, 2019. This

study was registered as UMIN000037704 on August 17, 2019 and was conducted in accordance with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the participants.

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