INTRODUCTION

Current literature offers scant information on mechanisms that cure patients suffering from hiccups, so when our team discovered a reliable method we subjected our breakthrough to rigorous investigation. The mechanism behind our method is simple: hiccups stop when the partial pressure of CO₂ in arterial blood (PaCO₂) reaches the same level as that in venous blood (PvCO₂), or approximately 50 mm Hg. Theoretically, these conditions will be consistently effective due to the connection to the body’s survival instinct (more on this later). Our goal in this article is not

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ORIGINAL ARTICLE

CO₂ retention: The key to stopping hiccups

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Abstract

Background: While investigating the mechanisms behind hiccups, our team discovered what could be the sufficient physiological conditions for terminating even persistent cases.

Methods: To investigate the role of CO₂ retention, a healthy male volunteer was asked to perform three kinds of rebreathing experiments using different materials: (I) a 20 L air-filled plastic bag, (II) a 20 L air-filled plastic bag with a 1.5 × 1.5 cm hole and (III) a 20 L oxygen-filled plastic bag. During each experiment, CO₂ level upon expiration (EtCO₂) and inspiration (InspCO₂) were measured until the volunteer gave up. Once the safety of this manoeuvre was demonstrated with the volunteer, we performed the technique using the materials from experiment (I) on two actual patients with persistent hiccups.

Results: In experiments (I) and (III), InspCO₂ increased from the beginning and reached almost the same level as EtCO₂ after 90 seconds. Both levels continued simultaneously increasing, finally reaching 56 mm Hg in (I) and 79 mm Hg in (III), respectively. In (II), both increased; however, after 120 seconds, EtCO₂ plateaued at 47 mm Hg and InspCO₂ at 37 mm Hg. In the actual patients, both CO₂ levels reached the same value of 35.9 mm Hg at 60 seconds and 37.0 mm Hg at 90 seconds, and hiccups stopped at 195 seconds and at 359 seconds when EtCO₂ reached 50 mm Hg and 53 mm Hg, respectively.

Conclusion: The study determined that to successfully obstruct the mechanisms causing hiccups, it is necessary that the level of InspCO₂ not only increases at the same level as EtCO₂, but also reaches approximately 50 mm Hg.

KEYWORDS
chemotherapy, hiccups, hypercapnia, paper bag rebreathing
to dismiss other methods, but rather to engage in an objective discussion on the physiological conditions that stop hiccups.

In reality, our method is simply a modified version of the paper bag rebreathing method. Paper bag rebreathing, once considered an effective treatment for hyperventilation, has lost its status as a clinical treatment in recent years. However, according to several previous reports, it has been revealed in experiments using felines that CO₂ inhalation suppresses the movements of the muscles associated with hiccups. This suggests that our method, which simply replaces the paper bag with an airtight plastic bag, could potentially be regarded as an appropriate treatment for hiccups.

This method is likely still regarded by many clinicians as questionable at best due to its resemblance to other similar home remedies and a lack of supporting evidence until now. We anticipate that the addition of objectively gathered data to the discussion will open the door for consideration of plastic bag rebreathing as a reliable clinical treatment.

We explored what transpires internally during plastic bag rebreathing by employing both volunteers and real hiccup patients to gauge the physiological conditions under which hiccups stop. Using our results, we will discuss the mechanism for stopping hiccups and the supporting theory behind our plastic bag rebreathing method.

2 MATERIALS AND METHODS

Currently there are only seven clinical records of patients with persistent hiccups cured by the plastic bag rebreathing method at our institution. However, we performed these cases using techniques based on years of empirical evidence, which can be summed up in the following three points:

1. Our plastic bag rebreathing method always stopped hiccups within 2–4 minutes without leading patients to suffocation.
2. Hiccups did not stop if the airtight seal of the plastic bag was broken during the treatment.
3. The CO₂ level—not the O₂ level—in the breath appeared to play a critical role in stopping hiccups.

Using this information, we conducted three experiments to observe what occurs in human bodies during plastic bag rebreathing. Before mentioning the study design, let us first outline the exact method, which we have termed the ‘Bucci Method’:

I. The Bucci Method is as follows:

1. A 20 L clear plastic bag (520 × 600 mm) is used in place of the standard paper bag.
2. The plastic bag is inflated with air.
3. The patient’s whole head is completely covered with the bag, ensuring that it does not cling to the patient’s nostrils, and an airtight seal is made around the patient’s neck.
4. The doctor constantly checks the airtightness of the patient’s plastic bag.
5. The patient calmly continues taking breaths as deeply as possible until the patient’s hiccups are completely resolved. During the process, the patient’s arterial oxygen saturation level must be closely monitored using a pulse oximeter.
6. Hiccups are usually cured within a few minutes. No patients have complained of experiencing any choking sensations.
7. Results from our two successful experiences with actual outpatients will be presented in the Results section.

II. Using the Bucci Method, we conducted three experiments in order to investigate the conditions within the plastic bag during the manoeuvre. We enlisted a 54-year-old healthy male 1.87 m in height and 76 kg in weight as a volunteer and performed the experiments as follows:

(1) Experiment 1: the volunteer held a CO₂ sensor in his mouth, and a 20 L plastic bag filled with air was placed over his head with an airtight seal around the neck. The EtCO₂ meter measured the value of CO₂ partial pressure in the expiratory gas (EtCO₂) as well as that in the inspiratory gas (InspCO₂). A pulse oximeter was attached to his finger to measure blood oxygen level (SpO₂) and heart rate (HR). Rebreathing in the plastic bag was to be continued for either 10 minutes, until SpO₂ went down below 90%, or until the volunteer gave up. The EtCO₂, InspCO₂, SpO₂ and HR were measured every 30 seconds until the end of the experiment.

The measuring instruments for EtCO₂, InspCO₂, SpO₂ and HR were an EtCO₂ meter (Microstream™; Medtronic, Minneapolis) and a multi-monitoring system (DS-8200; FUKUDA DENSII, Tokyo, Japan). Incidentally, it is generally thought that EtCO₂ can be considered a virtual representation of PaCO₂.

(2) Experiment 2: All conditions were the same as Experiment 1, but we cut a 1.5 × 1.5 cm hole in the plastic bag.

(3) Experiment 3: All conditions were the same as Experiment 1, but we filled the airtight plastic bag with 100% oxygen instead of air.

III. After successfully completing the three experiments, we enlisted the help of two real patients with persistent hiccups to observe when hiccups stopped using the same protocol as Experiment 1. The first patient was a male in his fifties who repeatedly suffered from persistent
hiccups due to chemotherapy; the second patient was a male in his sixties who had suffered from persistent hiccups for 1 month. We used video recording technology to demonstrate the successful treatment of an actual patient with hiccups. The study protocol was examined and approved by our Research Review Board (No. 16–1010, approved on Oct. 31, 2016). We obtained written permission from the patients to include anonymous information in our study, with the understanding that the patient’s privacy would be completely protected. Video footage of the first patient is posted online as a video on Youtube7 (first patient in the video).

3 | RESULTS

I. Details from two of the seven cases at our institution in which we employed the Bucci Method are presented below.

Case 1: In September 2016, a 67-year-old male who suffered from persistent hiccups for 7 days was referred to our clinic, although metoclopramide was repeatedly injected at the former clinic. He had tried various remedies listed on the Internet, such as sticking fingers in both ears, pressing on his diaphragm, alternating between deep breaths and holding his breath, rebreathing into a paper bag and so on—all in vain. The Bucci Method was performed using a 20 L air-filled plastic bag. After 2–3 minutes, the persistent hiccups were completely resolved without any discomfort.

Case 2: In November 2017, an 83-year-old healthy male who suffered from persistent hiccups for eight days was referred to our clinic. After administrating oxygen using an O2 mask with 3 L/min for about three minutes, a 20 L air-filled plastic bag was employed using the Bucci Method. It took 4 minutes 51 seconds until the hiccups stopped. SpO2 showed 100% at the start of the manoeuvre and 98% at the time the hiccups stopped.

The two cases cited above imply that the conditions 2–4 minutes in to the manoeuvre hold the key to stopping hiccups effectively. In both cases the CO2 level in the blood most likely increased, and Case 2 suggests that the O2 level in the blood has limited, if any, influence on the phenomenon.

II. The results of the three plastic bag rebreathing experiments were as follows:

1) Experiment 1 was stopped after 3 minutes 40 seconds when the volunteer gave up (Figure 1). InspCO2 gradually increased from the beginning, reaching almost the same level as EtCO2 at 1 minutes 30 seconds, whereupon both InspCO2 and EtCO2 continued to increase at an even pace before reaching 56 mm Hg. The duration from start to when EtCO2 reached 50 mm Hg was 2 minutes 30 seconds.

2) Experiment 2 was finished in the prerequisite time of 10 minutes even (Figure 2). InspCO2 gradually increased over 2 minutes but maintained a steady value of less than 40 mm Hg thereafter. EtCO2 also gradually increased over 2 minutes, at which point it maintained an almost constant value of 47 mm Hg. InspCO2 levels always remained below those of EtCO2 during this experiment, and the gaps between InspCO2 and EtCO2 were continuously identifiable. At the same time, SpO2 showed an almost straight line with a constant value of 97%.

3) Experiment 3 was aborted after 6 minutes 30 seconds when the volunteer gave up (Figure 3). The SpO2
levels remained at a constant 100%. However, both InspCO2 and EtCO2 saw continual increases from the onset with both eventually reaching 79 mm Hg. The duration from start to when EtCO2 reached 50 mm Hg was 2 minutes. Incidentally, InspCO2 reached the same value as EtCO2 at 1 minute 30 seconds, as was the case in Experiment 1.

III. In the two actual hiccup patients, InspCO2 reached the same value as EtCO2 at 1 minute in the former patient, and at 2 minutes 10 seconds in the latter. Hiccups stopped at 3 minutes 15 seconds when both EtCO2 and InspCO2 reached 50 mm Hg in the former,7 and at 5 minutes 59 seconds when both of them reached 53 mm Hg in the latter. At the time hiccups stopped, SpO2 showed 93% and 95%, respectively.

4 | DISCUSSION

We stumbled upon the observation that acute CO2 retention induced by plastic bag rebreathing resolves persistent hiccups. This discovery is actually quite similar to the results achieved by other Japanese researchers during experiments using felines when they indicated that CO2 inhalation suppresses the movements of the muscles associated with hiccups.2,3 Although formal medical treatments such as metoclopramide injections are recommended for persistent hiccups,4,9 our plastic bag rebreathing method is effective even for patients with metoclopramide-resistant hiccups. Initially we thought that mild hypercapnia would be sufficient in stopping hiccups, but after many failed experiments we gradually realized that for a stable outcome it is necessary to accumulate a substantial level of CO2 inside the body. To clarify the necessary conditions, we conducted these experiments using a plastic bag to deliberately induce hypercapnia.

As mentioned earlier, Experiment 1 revealed conditions leading to a successful case, and Experiment 2 simulated conditions that would cause a failed case. In Experiment 2, the volunteer was able to continue the plastic bag rebreathing for 10 minutes without any discomfort. On the other hand, in Experiment 3, even though SpO2 was kept at 100%, the volunteer could not continue the experiment for the same duration because of overheating. These three results demonstrate a number of important facts in human physiology: a high level of CO2 retention in our bodies can act as a trigger causing discomfort, such as our reaction to unbearable heat. However, before jumping to conclusions in defining what level of CO2 should be regarded as the threshold, further investigation into human physiology was necessary.

In what way did Experiment 2 differ from Experiments 1 and 3? Airtightness. Experiment 2 demonstrated that our respiratory ventilation system is so efficient that it can easily discharge CO2 even when given only a small slit for transference. Even the small gap between EtCO2 and InspCO2 indicates that PaCO2 is still smaller than PvCO2; in other words, there is a gap between PvCO2 and PaCO2 [Δ(PvCO2–PaCO2) > 0 mm Hg], and as long as Δ(PvCO2–PaCO2) is larger than zero, an individual can easily withstand hypercapnia for an extended period. But it is clear in Experiments 1 and 3 that Δ(PvCO2–PaCO2) lowered to zero at some point, because CO2 could not be discharged. Since PvCO2 is normally 48 mm Hg, the point at which Δ(PvCO2–PaCO2) became zero must be when EtCO2 as well as InspCO2 reached at least 48 mm Hg.

Incidentally, when hiccups stopped in two actual patients, EtCO2 as well as InspCO2 was 50 mm Hg in one patient and 53 mm Hg in the other. As we anticipated above, PaCO2 reached at least 48 mm Hg in both patients at the time hiccups stopped. PaCO2 reaching approximately 50 mm Hg must play a key role in stopping hiccups.

There are two kinds of blood gas sensors in the human body.10,11 The central chemoreceptors, located in the medulla, detect high levels of CO2 in the blood, while the carotid bodies detect low levels of O2.10,11 The central chemoreceptors are considerably more sensitive than the carotid bodies, so even small increases in CO2 produce large increases in ventilation volume.10 According to our rebreathing results with an air-filled 20 L plastic bag, 2 minutes in to the experiment the SpO2 level remained around 99%; however, InspCO2 and EtCO2 increased to about 50 mm Hg. In such conditions, the central chemoreceptors must have worked intensely while the carotid bodies remained quiet.10,11

It is assumed that hiccups are induced from afferent signals to the medulla through branches of the glossopharyngeal nerve distributed along the pharynx,2,12 and the signals strike a ‘hiccup centre’ likely located in the medullary reticular
formation,\textsuperscript{12,13} although the exact location has not yet been identified (Figure 4). The hiccup centre, once activated by the afferent signals, must then emit its own abnormal yet intermittent signal near the medullary inspiratory centre, in a pattern much like cardiac arrhythmia. Usually, the medullary inspiratory centre is controlled by the pneumotaxic centre located in the pons.\textsuperscript{14} However, this rogue signal can directly enter the medullary inspiratory centre without interference from the pneumotaxic centre of the pons. It is at this point that hiccups begin.

Speculation on why our manoeuvre is effective in curing hiccups is outlined in Figure 5. Our method produces conditions with high levels of both $\text{PaCO}_2$ and $\text{PvCO}_2$ (over 50 mm Hg) within a few minutes. Under these conditions, the central chemoreceptors would send strong alerts to the cerebrum that breaths have stopped and that proper measures should be taken immediately to survive.\textsuperscript{10,11} The alerts would suppress any opposing signals from the medulla and the pons, going straight to the muscles and nerves related to respiration to normalize breaths for survival. Eventually, the hiccup centre likely located in the medulla would also be suppressed,\textsuperscript{2,12,13} thereby resolving the hiccup problem.

What does it mean when $\Delta(\text{PvCO}_2 - \text{PaCO}_2)$ becomes zero (Figure 6)? We believe it represents the moment the brain senses that suffocation will occur despite high levels of $O_2$ remaining in an individual’s body. Under such conditions the brain will emit a stress signal to escape from the situation while the remaining $O_2$ is still sufficiently high. This leads us to believe that the high level of $CO_2$ retention, which is represented when both $\text{PvCO}_2$ and $\text{PaCO}_2$ exceed approximately 50 mm Hg, can trigger hiccups to stop. Since this reaction originates from our survival instinct, such conditions would theoretically terminate any and all hiccups without discrimination.

It is certainly understandable that clinical practitioners might be reluctant to introduce the Bucci Method because of the fear of accidental suffocation. Although our results demonstrate that a safe level of $O_2$ still remains in the blood at the time hiccups stop, we understand the importance of removing this fear for both clinicians and patients alike. One way this can be achieved is to administer $O_2$ to patients before starting treatment.

We believe our findings regarding the definitive conditions for stopping hiccups are a new discovery. Although it might be difficult at first to regard the Bucci Method as a serious option for treatment, understanding the correlation between the body’s survival instincts and stopping hiccups could open new horizons in our understanding of human physiology.

\begin{itemize}
\item \textbf{PaCO2 increases}
\item \textbf{Plastic bag rebreathing}
\item \textbf{1st alarm for high CO2}
\item \textbf{Chemoreceptors set off alarm}
\item \textbf{Hiccups are stopped}
\item \textbf{Ventilation volume increases}
\item \textbf{Medulla becomes silent and yields to cerebrum}
\item \textbf{2nd alarm for low O2}
\item \textbf{Carotid body sets off alarm}
\item \textbf{PaO2 decreases}
\item \textbf{Suffocation}
\item \textbf{Cheyne-Stokes respiration}
\end{itemize}
CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

Designed study and wrote the article: Obuchi
Collected data: Shimamura, Miyahara, and Fujimura
Conducted the study: Iwasaki

ETHICS

The study protocol was examined and approved by our Research Review Board (No. 16–1010, approved on Oct. 31, 2016). We obtained written permission from the patients to include anonymous information in our study, with the understanding that the patient’s privacy would be completely protected.

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