Original Article

Medullar impairment resolves hiccups

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Background: In a previous article we reported the time that hiccups stop as the instant when CO_2 levels in both expiratory gas ($EtCO_2$) and inspiratory gas ($InspCO_2$) reach approximately 50 mmHg. To support our findings, in this article we aim to clarify the precise values of the CO_2 level in arterial blood ($PaCO_2$) and venous blood ($PvCO_2$) during plastic bag rebreathing.

Methods: A healthy male volunteer was asked to perform a rebreathing experiment using a 20 L air-filled plastic bag. During the experiment, his blood oxygen saturation level (SpO_2), $EtCO_2$ and $InspCO_2$ were measured until the volunteer gave up. $PaCO_2$ and $PvCO_2$ were measured at the following four points: P_0, when the rebreathing started; P_1, when both $EtCO_2$ and $InspCO_2$ indicated the same value; P_2, when both reached 50 mmHg; and P_3, when SpO_2 dropped to 90%.

Results: $InspCO_2$ increased from the beginning and showed the same value as $EtCO_2$ at P_1. $PaCO_2$ at P_1 was almost the same value as both $InspCO_2$ and $EtCO_2$. After P_1, $InspCO_2$, $EtCO_2$ and $PaCO_2$ increased at the same rate, and at P_2, they reached the level of $PvCO_2$. After P_2, all four markers continued to show the same value as they gradually increased.

Conclusions: Creating conditions inside the body in which $PaCO_2$ increases to the same level as $PvCO_2$ will stop hiccups consistently. Although other physiological pathways to stop hiccups may exist, for a successful outcome it is important that the balance of power between the cerebellum and the medulla is drastically altered.

Keywords: Hiccups; medulla; carbon dioxide (CO_2)

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Introduction

Many people hold deep-seated beliefs surrounding home remedies for hiccups and often assume their method of choice will be equally effective for someone else despite a lack of supporting evidence (1). Rather than dismiss these remedies outright, as scientists, we instead embrace the challenge to reveal the underlying physiological mechanisms.

According to the results of our experiments employing our plastic bag rebreathing method, we have reported that the time hiccups stop must be when CO_2 levels in both expiratory gas ($EtCO_2$) and inspiratory gas ($InspCO_2$) reach approximately 50 mmHg (2). In addition, using the findings, we elicited that the CO_2 level in arterial blood ($PaCO_2$) should simultaneously reach approximately 50 mmHg at the time hiccups stop; however, there was only supportive data to imply our conjecture regarding $PaCO_2$ in the former report (2).

We conducted another experiment to further investigate what actually happens to blood CO_2 levels during plastic bag rebreathing. Using the results, we will discuss the

Table 1 Values of $InspCO_2$, $EtCO_2$, $PaCO_2$, $PvCO_2$, and SpO_2 from P_0 through P_3

Point (time, s)	P_0 [0]	P_1 [90]	P_2 [210]	P_3 [360]
$InspCO_2$ (mmHg)	0.0	39.1	50.0	61.9
$EtCO_2$ (mmHg)	35.0	39.1	50.0	61.9
$PaCO_2$ (mmHg)	43.6	39.8	48.2	61.0
$PvCO_2$ (mmHg)	47.5	48.2	50.1	61.9
SpO_2 (%)	97	99	97	88

$InspCO_2$, CO_2 level of inspiratory gas; $EtCO_2$, CO_2 level of expiratory gas; SpO_2, peripheral capillary oxygen saturation; $PaCO_2$, partial pressure of CO_2 in arterial blood; $PvCO_2$, partial pressure of CO_2 in venous blood.

physiological meanings behind reactions in the experiment, spotlighting the correlation between mimicking choking and stopping hiccups.

Methods

The study protocol was examined and approved by our Research Review Board (No. 17-0310, approved on March 10, 2017). An extension of the study period to the end of March 2019 was approved on April 3, 2018. Written consent was obtained from the volunteer prior to this experiment.

According to our former report, we knew $EtCO_2$ and $InspCO_2$ would show the same values at around 90 seconds in to the plastic bag rebreathing method when using a 20 L air-filled plastic bag (2). And if the airtight seal was not compromised, both $EtCO_2$ and $InspCO_2$ would exceed 50 mmHg before blood oxygen saturation level (SpO_2) dropped below 90%. Incidentally, the level of 50 mmHg in both $EtCO_2$ and $InspCO_2$ represents the point at which hiccups stopped in the two previous experiments with two patients suffering from persistent hiccups (2).

We enlisted a 55-year-old healthy male 1.87 m in height and weighing 77 kg as a volunteer for the experiment. An arterial line (A-line) was taken on his left wrist, and 1,500 units of heparin sodium was injected from the line. He held a CO_2 sensor in his mouth to measure both $EtCO_2$ and $InspCO_2$, and a 20 L clear plastic bag (520 mm × 600 mm) filled with air was placed over his head with an airtight seal around the neck. We attached a pulse oximeter on his left toe to measure SpO_2 and instructed him to rebreathe into the plastic bag for as long as possible. $EtCO_2$, $InspCO_2$, and SpO_2 levels were continuously measured until the end of the experiment. Arterial blood and venous blood were simultaneously taken at the following four points: P_0, when the plastic bag rebreathing started; P_1, when both $EtCO_2$ and $InspCO_2$ showed the same value; P_2, when both reached 50 mmHg; and P_3, when SpO_2 decreased to 90%. Arterial blood was taken through the A-line by a doctor, and venous blood was taken from his right arm by a nurse. These blood samples were quickly analyzed using a blood gas analyzer (ABL735; Radiometer, Tokyo, Japan) (3). The measuring instruments for $EtCO_2$, $InspCO_2$ and SpO_2 were an $EtCO_2$ meter (Microstream™; Medtronic, Minneapolis, USA) and a multi-monitoring system (DS-8200; FUKUDA DENSHI, Tokyo, Japan) (4,5).

Results

P_1 occurred at 90 s from the start, P_2 at 210 s, and P_3 at 360 s, respectively (*Table 1*). Incidentally, SpO_2 levels were recorded every 15 seconds during the experiment, registering at 91% at 345 seconds and 88% at 360 seconds. SpO_2 at P_3 was recorded as not 90% but 88% in *Table 1*.

$InspCO_2$ sharply increased from P_0 to P_1 and then lost speed after reaching the same level as $EtCO_2$, both slowly continuing to rise (*Figure 1*). $EtCO_2$ was almost plateaued from P_0 to P_1, but then began to gradually increase along with $InspCO_2$.

$PaCO_2$ decreased slightly from P_0 to P_1 (*Figure 2*). After showing almost the same value as both $EtCO_2$ and $InspCO_2$ at P_1, it then began to gradually increase along with $EtCO_2$ and $InspCO_2$. On the other hand, $PvCO_2$ very slightly increased or almost plateaued from P_0 to P_2, at which point it then gradually increased along with the other three parameters.

Discussion

Since hiccups are usually self-limiting, they are harmless for most people. However, in rare cases hiccups can become severe, such as patients with cancer undergoing

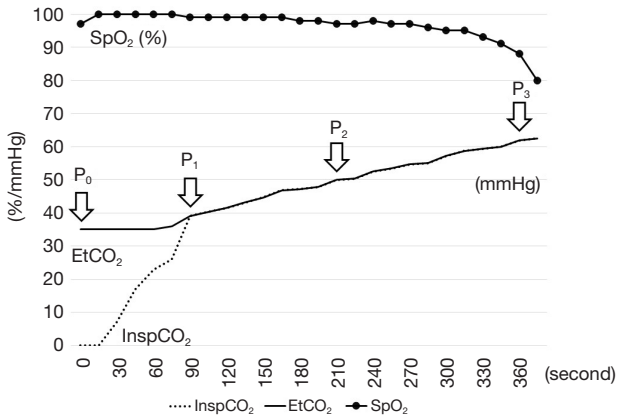

Figure 1 Graph of $InspCO_2$, $EtCO_2$ and SpO_2 during our plastic bag method. Both arterial blood and venous blood were simultaneously taken at P_0, P_1, P_2 and P_3. $InspCO_2$, CO_2 level of inspiratory gas; $EtCO_2$, CO_2 level of expiratory gas; SpO_2, Peripheral capillary oxygen saturation.

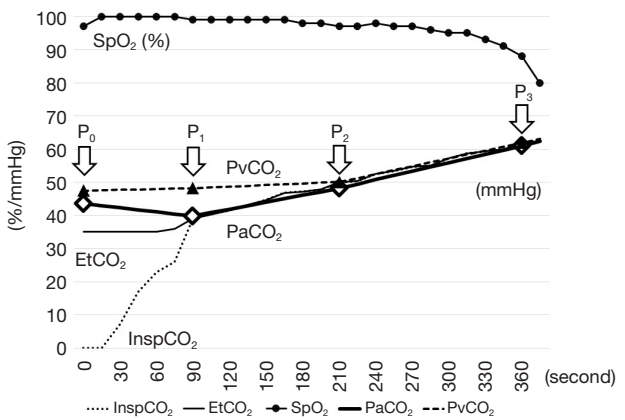

Figure 2 Graph of $InspCO_2$, $EtCO_2$, SpO_2, $PaCO_2$ and $PvCO_2$ during our plastic bag method. $PaCO_2$ showed the same value as both $InspCO_2$ and $EtCO_2$ at P1. $PaCO_2$ reached the same value as $PvCO_2$ at P_2. Four parameters increased in the same degree after P_2. $InspCO_2$, CO_2 level of inspiratory gas; $EtCO_2$, CO_2 level of expiratory gas; SpO_2, peripheral capillary oxygen saturation; $PaCO_2$, partial pressure of CO_2 in arterial blood; $PvCO_2$, partial pressure of CO_2 in venous blood.

chemotherapy; about 4–10% of cancer patients on chemotherapy (another research group has reported it was about 40% of them) suffer from severe chronic hiccups (6-8). Hiccups that continue beyond 48 hours are considered persistent, and episodes longer than 2 months are termed intractable (1). A problem for patients with persistent hiccups is that not only home remedies, but medical interventions are also often ineffective (1,7,8). From this point of view, evidence that our plastic bag rebreathing method consistently cured a number of patients with persistent hiccups could offer clues behind the mechanisms at work (2).

P_1 and P_2 are of significant physiological importance in our experiment. P_1 is the point at which not only $InspCO_2$ reached the same value as $EtCO_2$, but the point at which $PaCO_2$ reached almost the same value as well; namely, $InspCO_2 = EtCO_2 = PaCO_2$. We think this phenomenon represents the moment that the concentration of CO2 in the air inside the bag reaches the same value as $PaCO_2$; no longer is there a pressure gradient between arterial blood and lung air. After P1, once CO_2 is expelled from the lung into the air inside the bag through expiratory gas, the same volume of CO_2 begins infiltrating arterial blood through inspiratory gas. We can deduce that the duration from P_0 to P_1 depends on the size of plastic bag: the smaller plastic bag, the shorter the duration. And if no plastic bag is employed (as in the case of holding one's breath), the period is theoretically very short. The plastic bag thus works to supplement lung capacity in our rebreathing method.

P_2 is the point that PaCO2 reached almost the same value as $PvCO_2$; namely, $InspCO_2 = EtCO_2 = PaCO_2 = PvCO_2 =$ approximately 50 mmHg. This phenomenon means that the concentration of CO_2 in the entire bloodstream is equalized. After P_2, there is no longer a CO_2 pressure gradient between $PvCO_2$ and $PaCO_2$ [$\Delta(PvCO_2 - PaCO_2) = 0$ mmHg], and CO_2 accumulates in the body without being discharged. However, a sufficient amount of O_2 still remains in the air and blood until P_3.

What does P_2 mean physiologically? Originally, P_2 was considered the point at which hiccups stopped. But the experiment revealed that P_2 also represents the point at which $\Delta(PvCO_2 - PaCO_2)$ became 0 mmHg. The period between P_2 and P_3, the dangerous point at which SpO_2 began sharply dropping, must then represent what the brain feels is the last chance to escape from the situation in order to survive. During this period the brain must emit intense signals to take in fresh air before suffocation occurs.

Normally, breathing is controlled by both the cerebellum and the medulla (9). The cerebellum allows us to consciously control our breathing when necessary, but the medulla-controlled autonomic nervous system holds a clear power dominance. In fact, we can only continue holding our breath or hyperventilating for a short time before the medulla makes us unbearably uneasy and forces

us to quit. The medulla usually has dominance over the cerebellum in terms of breathing control, but that is not the case when it comes to facing to a life-threatening crisis. Imagine a scenario in which we suddenly feel O_2 deficiency while under water. During this situation, if the medulla worked normally, the autonomic nervous system would force us to begin breathing even under water. However, we can consciously hold our breath until we surface because the cerebellum orders us to keep holding our breath for survival. The cerebellum is clearly able to dominate over the medulla in such a crisis. This begs an important question: does the cerebellum take control over the medulla, or is the medulla weakened through external factors?

Before answering the question, an important correlation should be made between the medulla and the phenomenon of human hiccups (10). It is believed that the epicenter of hiccup production is located in the medulla, and although its exact location is still unknown, there are a number of supporting reports that medullary tumors caused persistent hiccups (1,10-13). If the hiccup epicenter is located inside the medulla, this means that when the hiccup epicenter emits rogue signals the medulla automatically responds. The medulla's response is misinterpreted by the body as normal orders from the medulla, which implies that the cerebellum does not control hiccups.

According to our experiments, hiccups should always stop around P_2, at which point the brain must send off a strong alarm for survival. The conditions around P_2 are similar to the above underwater scenario. If the medulla only yielded respiration control to the cerebellum but continued to function, the hiccup epicenter would also remain active. On the contrary, if the medulla became completely incapacitated, the hiccup epicenter inside the medulla would also be switched off. Therefore, the answer to the question regarding the power balance between the cerebellum and the medulla in a crisis is that the medulla weakens. In its weakened state, signals from the autonomic nervous system would no longer interfere with orders from the cerebellum. We believe hiccups will stop if we are able to create a situation that tricks the medulla into thinking it is faced with a crisis, as seen at P_2. The medulla including the hiccup epicenter and primitive functions of respiration control will be strongly suppressed.

There are countless home remedies for hiccups in the world (1,13); in Japan, it is believed that hiccups will stop when the person is startled. Many of them sound unreliable or unscientific, but after our experiments, we have come to realize that some remedies (such as holding one's breath) may have some supporting evidence behind them. Although other physiological pathways to stop hiccups may exist, in theory hiccups could be immediately resolved if human lung capacity was sufficient enough to allow $PaCO_2$ and $PvCO_2$ to reach approximately 50 mmHg [and $\Delta(PvCO_2 - PaCO_2) = 0$ mmHg] while holding one's breath. Although physical restrictions render this method impossible for most people, the same result can be achieved by supplementing lung capacity with an airtight plastic bag. But it is important that the balance of power between the cerebellum and the medulla is drastically altered.

We believe the simple conclusion is that hiccups will always be resolved when functions of the medulla drastically weaken, such as when facing a crisis. It is our hope that these findings could be the catalyst to exploring a new horizon in human physiology.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study protocol was examined and approved by our Research Review Board (No. 17-0310, approved on March 10, 2017). Written consent was obtained from the volunteer prior to this experiment.

References

1. Chang FY, Lu CL. Hiccup: mystery, nature and treatment. J Neurogastroenterol Motil. 2012;18:123-30.
2. Obuchi T, Shimamura S, Miyahara N, et al. CO2 Retention: The key to Stopping Hiccups. Clin Respir J 2018. [Epub ahead of print].
3. Radiometer. Available online: https://www.radiometer.co.jp. Accessed May 2, 2018.
4. Microstream-capnography. Available online: http://www.medtronic.com/covidien/en-us/index.html. Accessed May 2, 2018.
5. DS-8200. Available online: http://www.fukuda.com/index_usa.html. Accessed May 2, 2018.
6. Porzio G, Aielli F, Verna L, et al. Gabapentin in the treatment of hiccups in patients with advanced cancer: a 5-year experience. Clin Neuropharmacol 2010;33:179-80.

7. Takahashi T, Hoshi E, Takagi M, et al. Multicenter, phase II, placebo-controlled, double-blind, randomized study of aprepitant in Japanese patients receiving high-dose cisplatin. Cancer Sci 2010;101:2455-61.
8. Liaw CC, Wang CH, Chang HK, et al. Cisplatin-related hiccups: male predominance, induction by dexamethasone, and protection against nausea and vomiting. J Pain Symptom Manage 2005;30:359-66.
9. Critchley HD, Nicotra A, Chiesa PA, et al. Slow breathing and hypoxic challenge: cardiorespiratory consequences and their central neural substrates. PLoS One 2015;10:e0127082.
10. Becker DE. Nausea, vomiting, and hiccups: a review of mechanisms and treatment. Anesth Prog 2010;57:150-6; quiz 157.
11. Pechlivanis I, Seiz M, Barth M, et al. A healthy man with intractable hiccups. J Clin Neurosci 2010;17:781-3.
12. Gambhir S, Singh A, Maindiratta B, et al. Giant PICA aneurysm presenting as intractable hiccups. J Clin Neurosci 2010;17:945-6.
13. Kumar A. Gag reflex for arrest of hiccups. Med Hypotheses 2005;65:1206.

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