

Peer review file

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Overview:

The submitted manuscript is an expanded study regarding the use of CO₂ in obstinate singultus. While the approach is not fundamentally new the authors provide a target-guided strategy (i.e. inducing normoxic hypercapnia as to abolish the venous-arterial CO₂ gradient) that appears to be effective. In addition, they suggest a plausible patho-physiologic explanation as to why this approach might work. The submission is dichotomous; the experimental part is very interesting and must –in my view- be published while the theoretical explanations provided are highly speculative and need substantial rework and expansion, should they be included.

Language: not acceptable. Editorial rewrite is mandatory.

Title: Gas-Based Treatment is not explanatory; could be anything.

Conflict of interest: In the text, the authors allude to a patent application; that might be a clear COI.

Comment 1: *Our team found that hiccups are stopped when exposed to acute hypercapnia.*

The observation is hardly new. Contrary to the view repeatedly expressed in modern literature that the method was first suggested by the Americans Henderson, Sword or Sheldon, the Briton Hewer or the Austrian Doppler, the origin of the observation appears to be French and was first published in 1892 by Paris pharmacist Henri Bocquillon-Limousin in his, Formulary of new drugs and new medications. For a history of the use

of CO₂ in obstinate singultus please refer to: Singultus, paper-bag ventilation, and hypercapnia. J Hist Neurosci. 2020 Jan 8:1-13. doi: 10.1080/0964704X.2019.1708161. [Epub ahead of print]

Reply 1: Thank you for pointing it out. Please see LL24-26. Also, we added citation of the paper that you suggested in the discussion part. Thank you.

Comment 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*

This is the core assumption of the authors; however, it is an unproven apodictically statement. They did not compare various gas mixtures to come to the conclusion that a particular one is superior.

Reply 2: Thank you for your good question. I am afraid I may need to explain the cultural differences in medical research fields between Japan and the US in order to persuade you to believe me. Actually, my team does not have any research funds at all. I had to pay about USD 400 of my own money to get the combination gas and the gas tank. If I had tried to get various gas mixtures, that cost would have been much greater. Compared with US thoracic surgeons, Japanese surgeons are generally very humble, with about a tenth of their incomes, because Japanese doctors are regarded as a kind of public servant. Moreover, Japanese doctors, like me, working for private hospitals have no qualifications to get any research funds. If I could have sufficient research funds, I could do as you mentioned. But this is the best that we can do, unfortunately. I would appreciate it if you could understand my situation for this research. Thank you.

Comment 3: *We developed a combination gas consisting of 10% CO₂ and 90% O₂ called “Bucci gas” (patent pending; Bucci refers to the wisdom of Buddha)*

I am not knowledgeable in the area of patent law but the authors need to be aware that the name *carbogene* for the mixture of CO₂ and oxygen was introduced by chemist, Paul Poiré (1832–1900) and his partner, pharmacist Adéodat Dufourmantel (pharmacien en chef des hôpitaux, à Amiens; *1826). They owned a patent (Brevet # 58807) for CO₂ production since 1863.

Reply 3: Thank you for the information. In fact, I submitted this system (not the combination gas itself) for patent application, paying the cost of USD 3000 myself. However, this is not to make money but to protect my idea until my paper is accepted to a publisher. If I wanted to make some money using it, I would have had to pay another USD 5000 to take screening to be an actual patent. But this would have been ridiculous for me to pay. Incidentally, Bucci is my nickname when I was a child, and is also in memory of my deceased baby. Since it has little meaning in this study, I deleted it. Please see LL 55-58. Thank you.

Comment 4: *From August 2019 to February 2020, a total of 23 patients with long-term intractable hiccups were treated with Bucci gas at our institution.*

Obstinate hiccup is a rather rare symptom, at least in the Caucasian population. When we performed our study, it was rather difficult to recruit our patients and we had the support of national radio. It would be advantageous to explain how they managed to find such a considerable number of patients in such a short period of time. Is St. Mary hospital the leading hiccup center in Japan?

Reply 4: Thank you for your question. Actually, I agree with you; there were far more patients than I expected. Fortunately, newspaper, TV and the Internet worked well by chance. However, as a US researcher reported, the number of those patients seems to be larger than people actually think. Incidentally, our hospital is far from being the leading hiccup center in Japan. Our team all members are just thoracic surgeons, not physicians nor researchers. Thank you.

Comment 5: *standard medication.*

Please elaborate if possible on what is meant by standard medication.

Reply 5: Please see LL80-81. Thank you.

Comment 6: *If patients agreed, a blood test was performed to measure the partial pressure of CO₂ in venous blood.*

Please indicate the exact number of patients agreeing.

Reply 6: Please see L29, L77, L112 and Table 1. While waiting for the decision letter, we had more patients. The number of patients was updated in the latest draft; it increased from 26 cases (23 patients) to 35 cases (26 patients). The number of patients agreeing to a blood test was 20. Please see L119. Thank you.

Comment 7: *mean duration of hiccups was 7.5 years.*

Please also provide SD and range.

Comment 8: *Hiccups were successfully stopped in all patients in a mean time of 5.6 minutes.*

Please also provide SD and range.

Reply 7-8: I did so. Please see L31, L37, L39, LL114-116, and LL126-128. Thank you.

Comment 9: *Hiccups are involuntary movements triggered from afferent signals through the glosso-pharyngeal nerve.*

Certainly not exclusively via afferents of the CN IX.

Reply 9: Please see LL132-134. Thank you.

Comment 10: *In addition, our results seem to strongly support the fact that the fight-or-flight response is related to stopping hiccups because tachypnea and a significant heart rate increase were clearly observed in all cases where hiccups were stopped.*

The brain equates the CO₂ retention in our procedure with CO₂ retention in a person whose breathing has actually stopped. The brain then reacts to the perceived impending O₂ deficiency by activating the sympathetic nervous system and fight-or-flight response to escape danger.

The view that sympathetic activation is therapeutic in obstinate hiccup is certainly interesting and new but contradicting more traditional views. It is not possible at this stage to determine the validity of many contradictory views, but such views must be mentioned/discussed.

For review on parasympathetic activation in hiccup, please refer to: Treatment of hiccup by vagal maneuvers. J Hist Neurosci. 2015;24:123-36 and also mention in the discussion the use of vagus stimulators for same purpose.

Furthermore in a fight-or-flight response both components of the autonomic nervous system are activated, and occasionally the parasympathetic component dominates in the initial period (albeit the final dominant is sympathetic); proof of parasympathetic

component transitory dominance is reflected in many vulgar expressions such as “ I peed in my pants, so scared I was”.

Please review/revise the paragraph.

Reply 10: I completely revised the paragraph based on your suggestions and your knowledge. Please see LL141-175. Thank you.

Comment 11: Please remove unwarranted qualifiers such as strongly support; suggest is a better descriptor.

Reply 11: Thank you for your good suggestion. I deleted it.

Reviewer’s conclusion: The experimental part of the manuscript is very interesting and certainly needs to be published (with some minor modifications). The mechanistic explanation is also interesting but highly speculative and not supported (or contradicted) by the data. It needs significant work and additional literature reading before it can be put forward. I suggest to stick with the clinical work done and publish it as a small communication while the mechanism part should be worked on and possibly resubmitted in due time.

Reply: Thank you for your comment. I completely revised my paper based on our clinical work. Please see LL171-197. Thank you.