

Reperfusion injury to ischemic medullary brain nuclei after stopping continuous positive airway pressure-induced CO₂-reduced vasoconstriction in sleep apnea

J. Howard Jaster

Department of Medicine, London Corporation, Kuala Lumpur, Malaysia

Correspondence to: J. Howard Jaster, MD. Department of Medicine, London Corporation, 159 Capital Square, Kuala Lumpur 50100, Malaysia. Email: harbert38104@yahoo.com.

Comment on: Schwarz EI, Stradling JR, Kohler M. Physiological consequences of CPAP therapy withdrawal in patients with obstructive sleep apnoea—an opportunity for an efficient experimental model. *J Thorac Dis* 2018;10:S24-S32.

Turnbull CD. Intermittent hypoxia, cardiovascular disease and obstructive sleep apnoea. *J Thorac Dis* 2018;10:S33-9.

Submitted Apr 23, 2018. Accepted for publication May 07, 2018.

doi: 10.21037/jtd.2018.05.70

View this article at: <http://dx.doi.org/10.21037/jtd.2018.05.70>

The Journal recently published two papers (1,2), which described from different perspectives the physiological consequences of withdrawing continuous positive airway pressure (CPAP) from sleep apnea patients—both papers ignoring the medullary brain ischemia which results from untreated sleep apnea, and which is exacerbated by CPAP therapy, and which is further provoked by CPAP withdrawal, and which probably becomes an etiological focus for cardiac arrhythmias and sudden death. An experimental model involving withdrawal of CPAP from sleep apnea patients may therefore have inherent dangers.

After sleep apnea becomes established, pulmonary gas exchange is chronically worsened, leading to a significantly increased risk of adverse events manifested by the heart, which include cardiac arrhythmias and sudden death, and whose cryptic origin probably lies in the brain medulla (3-6). Treatment by CPAP improves pulmonary gas exchange and increases myocardial oxygenation. But during CPAP, blood flow in the brain is probably reduced, causing adverse effects.

How can that be possible?

Carbon dioxide is a potent dilator of brain vasculature, thereby increasing blood flow to the brain. When ventilation is increased, even if only to improve it back toward normal from a depressed steady-state level, the alveolar partial pressure of carbon dioxide is decreased, likely resulting in a converse relative vasoconstriction in the

brain, thereby reducing blood flow in the brain, especially in pertinent watershed areas like the solitary tract nucleus of the medulla. In normal physiology this is demonstrated impressively by the ability of hyperventilation to induce loss of consciousness.

What difference does it make if there is a slight vasoconstriction in the brain and slightly reduced blood flow? People with normal brains seem to tolerate such changes without difficulty.

In patients with sleep apnea, arterial carbon dioxide may not seem sufficiently reduced by externally applied respiratory therapy to cause even relative vasoconstriction in the brain, but a small reduction in carbon dioxide may be very significant statistically over a population of patients in the overall context of pathophysiology rather than normal physiology. When blood flow is decreased to an area that is already ischemic like the solitary tract nucleus, the ischemia will likely worsen and cause secondary effects related to its normal function which includes regulation of heart rate, rhythmicity, and contractility through its efferent (downstream) output pathway via the dorsal motor nucleus of the vagus nerve.

Why is the solitary tract nucleus of the medulla considered to be 'already ischemic' at the time CPAP is initiated to treat sleep apnea?

In recent years sudden unexpected death has been associated

with many types of small and pathologically benign medullary brain lesions like demyelination plaques—largely asymptomatic until they caused sudden death (7-10). Many such medullary lesions, typically without hemorrhage or mass effect, have in themselves been previously considered relatively harmless—in cases where they have been known to be present. Some not known to be present during life were discovered at autopsy in cases where no other cause of death could be identified.

And significantly, in heart failure and in sleep apnea (which often co-exist), sudden death has also been associated with medullary autonomic ischemic lesions, especially involving the solitary tract nucleus (11,12). These latter are probably not directly caused by cerebrovascular disease, or by the defective ventilation of sleep apnea, but rather by highly increased sensory afferent (upstream) vagal stimulation from the heart—which is in turn induced by cardiac ischemia and its resultant worsened cardiac performance, which together may be caused in part by the defective ventilation of sleep apnea. Sensory afferent (upstream) vagus nerve stimulation terminates at the solitary tract nucleus in the medulla, where the increased metabolic requirements associated with intense neurotoxic stimulation converge with a limited watershed vasculature to contribute to the formation of focal ischemic lesions. This constellation of events is believed to trigger sudden death by a mechanism which is unknown, but may be efferent (downstream) arrhythmogenic through the dorsal motor nucleus of the vagus nerve.

Evidence of the insidious influence on the brain of changing carbon dioxide levels may be seen in the somewhat different results obtained from two recent major clinical trials (13,14) using different forms of respiratory therapy to treat sleep apnea. In the SAVE trial using CPAP (13), the patients' airways were simply maintained in a more open position, allowing improved ventilation entirely through the patients' own breathing efforts. In the SERVE-HF adaptive servo-ventilation trial (14), airway maintenance was achieved together with mechanical inspiratory assistance. In the adaptive servo-ventilation study group the degree to which pulmonary ventilation and thus gas exchange were assisted was significantly greater than in the CPAP study group. In the CPAP study group (13) there was no net change in the incidence of sudden death compared to the control group.

In contrast, the adaptive servo-ventilation trial was halted (14) in progress when more patients in the study group were dying compared to the control group (15). Intended to improve oxygenation and gas exchange in

ischemic myocardial tissue, adaptive servo-ventilation may have paradoxically and perversely worsened circulation in ischemic medullary brain nuclei which are probably just as important in causing sudden death, and where the damaging effects of decreased carbon dioxide levels seem to outweigh any beneficial effects of increased oxygenation in the myocardium.

Schwarz *et al.* (1) (on page S28) mentioned that cardiac arrhythmias and sudden death are associated with sleep apnea, and that CPAP withdrawal led to cardiac repolarization abnormalities. I have suggested that when CPAP or adaptive servo-ventilation stops at the end of the night (short-term) or at the termination of therapy (long-term), two pathophysiological events may collide to induce cardiac arrhythmias. (I) The heart no longer receives the direct benefit of increased oxygen and improved pulmonary gas exchange. (II) Reperfusion injury occurs in the solitary tract nucleus because vasoconstriction has stopped.

In my opinion, CPAP became the 'gold standard therapy for sleep apnea' (a term used by Schwarz *et al.*) (1) in part because it intuitively made sense to both patients and physicians that medical problems caused by impaired breathing could be resolved by improved breathing. However, the pathophysiology of sleep apnea has turned out to be anything but intuitive (16). And the SAVE trial results (13), discussed in some detail by Turnbull (2), characterized and quantified many aspects of sleep apnea that are unimproved by CPAP.

Consistent with the 2016 research report of Schwarz and others (17) the critical anatomical focus of ischemia in the clinical setting of sleep apnea is not the myocardium, but the brain medulla (12). And the adaptive servo-ventilation investigators in 2018 (18) have reported these additional findings from their original trial: 'In patients with systolic heart failure and central sleep apnea, addition of adaptive servo-ventilation to guideline-based medical management had no statistically significant effect on cardiac structure and function, or on cardiac biomarkers, renal function and systemic inflammation over 12 months. The increased cardiovascular mortality reported in SERVE-HF may not be related to adverse remodeling or worsening heart failure'.

In the clinical setting of sleep apnea, confounded by cardiac arrhythmias and sudden death, both Schwartz and the adaptive servo-ventilation investigators have concluded that the focus of the etiological problem is not in the heart. In contrast, neuropathology reports confirm that the focus of the etiological problem is in the brain medulla. When this collection of research findings is taken together, there

are no inconsistencies or contradictions.

Why are we having so much difficulty connecting these dots?

Additional research about cardiac arrhythmias in the setting of CPAP withdrawal is needed—and this need has been previously implied. Indeed, in 2016 the report by Schwarz and others (17) that myocardial ischemia did not occur following CPAP withdrawal was accompanied by an editorial (19) warning of other less quantified dangers of withdrawing CPAP. The editorial correctly acknowledged the validity and importance of the research done by Schwarz and others (17). Nonetheless, it was titled with this rhetorical question, ‘Is the heart still in danger after stopping CPAP?’ The editorialist was concerned that the answer may be ‘yes’—and so am I.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

- Schwarz EI, Stradling JR, Kohler M. Physiological consequences of CPAP therapy withdrawal in patients with obstructive sleep apnoea—an opportunity for an efficient experimental model. *J Thorac Dis* 2018;10:S24-S32.
- Turnbull CD. Intermittent hypoxia, cardiovascular disease and obstructive sleep apnoea. *J Thorac Dis* 2018;10:S33-9.
- Jaster JH. Ischemic Lesion Formation in Solitary Tract Nuclei During Central Sleep Apnea With Heart Failure. *Circ J* 2016;80:1047.
- Jaster JH. Phrenic Nerve Stimulation – and Chorda Tympani Nerve Stimulation – May Prevent Lethal Cardiac Arrhythmias During Sleep Apnea with Heart Failure. *Int J Neurology Res* 2017;3:323-6.
- Jaster JH. Medicine in the future - with subspecialists in medullary neurology and brain dentistry. *World J Neurol* 2015;5:107-12.
- Jaster JH. Interfacing pathophysiology of respiratory sleep disorders, cardiac dysfunction, and focal autonomic medullary brain ischemia. *J Thorac Dis* 2015;7:E646-7.
- Jaster JH, Porterfield LM, Bertorini TE, et al. Cardiac arrest following vertebrobasilar stroke. *J Tenn Med Assoc* 1995;88:309.
- Jaster JH, Porterfield LM, Bertorini TE, et al. Stroke and cardiac arrest. *Neurology* 1996;47:1357.
- Jaster JH, Smith TW. Arrhythmia mechanism of unexpected sudden death following lateral medullary infarction. *Tenn Med* 1998;91:284.
- Jaster JH, Fitzek S, Fitzek C, et al. Myocardial injury after hemorrhage into the lateral medulla oblongata. *Neurology* 2001;57:1145.
- De Caro R, Parenti A, Montisci M, et al. Solitary tract nuclei in acute heart failure. *Stroke* 2000;31:1187-93.
- Parenti A, Macchi V, Snenghi R, et al. Selective stroke of the solitary tract nuclei in two cases of central sleep apnoea. *Clin Neuropathol* 2005;24:239-46.
- McEvoy RD, Antic NA, Heeley E, et al. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. *N Engl J Med* 2016;375:919-31.
- Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. *N Engl J Med* 2015;373:1095-105.
- ResMed. ResMed provides update on phase IV SERVE-HF study of adaptive servo-ventilation (ASV) therapy in central sleep apnea and chronic heart failure. San Diego, CA: May 13, 2015. Available online: <https://www.resmed.com/us/en/consumer/newsandinformation/news-releases/2015/resmed-provides-update-on-phase-iv-serve-hf-study-of-adaptive-servo-ventilation-therapy.html>
- Jaster JH. Medullary neuropathology in sleep apnoea. *Respirology* 2017;22:829.
- Schwarz EI, Schlatzer C, Stehli J, et al. Effect of CPAP Withdrawal on myocardial perfusion in OSA: A randomized controlled trial. *Respirology* 2016;21:1126-33.
- Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnoea in systolic heart failure: results of the major substudy of SERVE-HF. *Eur J Heart Fail* 2018;20:536-44.
- Ando S. Is the heart still in danger after stopping CPAP? *Respirology* 2016;21:980-1.

Cite this article as: Jaster JH. Reperfusion injury to ischemic medullary brain nuclei after stopping continuous positive airway pressure-induced CO₂-reduced vasoconstriction in sleep apnea. *J Thorac Dis* 2018;10(Suppl 17):S2029-S2031. doi: 10.21037/jtd.2018.05.70