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Review Article

CO_2-related vasoconstriction superimposed on ischemic medullary brain autonomic nuclei may contribute to sudden death

J. Howard Jaster [a], Josef Zamecnik [b], Aldo Bruno Giannì [c,d], Giulia Ottaviani [d,*]

London Corporation, 1655 Harbert Avenue, Memphis, TN 38104, USA
Department of Pathology and Molecular Medicine, 2nd Faculty of Medicine, Charles University, 11636 Prague, Czech Republic
Maxillofacial and Dental Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, 20122 Milan, Italy
"Lino Rossi" Research Center, Department of Biomedical, Surgical and Dental Sciences, University of Milan, 20122 Milan, Italy

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ABSTRACT

Introduction: In 2015, a multinational randomized controlled phase IV clinical trial of adaptive servoventilation for the management of heart failure with central sleep apnea was halted in progress because more patients in the study group were dying than in the control group. One year later, another large clinical trial reported results on the effectiveness of continuous positive airway pressure (CPAP) in preventing sudden death and other cardiovascular events such as heart attack and stroke in patients with preexisting vascular disease as well as obstructive sleep apnea.
Background: Sudden unexpected death has been associated with many types of small and nonmalignant medullary brain lesions, like demyelination plaques — largely asymptomatic until they caused sudden death. 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.
Discussion: Why did not the improved pulmonary ventilation and subsequently improved gas exchange provided during the CPAP and servoventilation clinical trials help to resolve any ischemic lesions that may have been present both in the heart and in the medulla, thereby tending to normalize interactions between the vagal neural structures and the heart? CO_2 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 watershed areas like the solitary tract nucleus. In normal physiology, this is demonstrated impressively by the ability of hyperventilation to induce loss of consciousness.
Conclusions: The findings of several clinical trials recently reported, taken together with neuropathology case studies reported elsewhere, suggest that additional research is warranted in regard to the mechanisms by which focal medullary autonomic brain ischemia may be related to sudden death in general medical illnesses — and how it may additionally be influenced by changes in arterial CO_2 levels.

1. Introduction

1.1. Ground zero

In 2015, a multinational randomized controlled phase IV clinical trial of adaptive servoventilation (ASV) for the management of heart failure with central sleep apnea (CSA) was halted in progress because more patients in the study group were dying than in the control group [1]. It seems that more than a few physicians around the globe were stunned and confounded by the news.

Competing interests: none.

* Corresponding author at: Centro di Ricerca "Lino Rossi", Dipartimento di Scienze Biomediche, Chirurgiche ed Odontoiatriche, Università degli Studi di Milano, Via della Commenda, 19-20122 Milano, Italy. Tel.: +39 02 50320819; fax: +39 02 50320823.
E-mail addresses: Giulia.Ottaviani@unimi.it, Giulia.M.Ottaviani@uth.tmc.edu (G. Ottaviani).

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The study group of patients had nocturnally been receiving pulses of pressurized air into the upper airway, synchronized to discharge during spells of apnea which occurred during sleep and which were considered to result from central nervous system causes. The therapy was simply an attempt to replace the patients' own respiratory efforts, which had intermittently ceased for the duration of each apnea spell. It was surmised that the respiratory therapy would help to maintain pulmonary gas exchange that had been impaired as a result of the apnea spells. It was hoped that with more normalized gas exchange, the patients would enjoy a variety of benefits and be less likely to experience sudden death — an adverse event that had been recognized to occur at greater frequency in patients who had heart failure with central sleep apnea. To many observers, the trial results as reported in the *New England Journal of Medicine* that September 2015 defied logic, leading some to question the design, methodology, and execution of the trial — and therein spawning a cacophony of letters to the editor [2] and opinion papers in other journals [3–7].

1.2. Grounded again

One year later, in 2016, the *New England Journal of Medicine* [8] reported on another large clinical trial that had studied the effectiveness of continuous positive airway pressure (CPAP) in preventing sudden death and other cardiovascular events such as heart attack and stroke in patients with preexisting vascular disease as well as obstructive sleep apnea. The trial investigators concluded that CPAP had no such effectiveness; however, the trial was able to proceed to completion with both the study group and the control group similarly affected by sudden death and other new cardiovascular events.

1.3. Background

In recent years, sudden unexpected death has been associated with many types of small medullary brain lesions, like demyelination plaques — largely asymptomatic until they caused sudden death [9–20]. 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 cases of medullary lesions, 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, sudden death has also been associated with medullary autonomic ischemic lesions, especially involving the solitary tract nucleus [21,22].

Because these latter have been more anatomically specific to a neuronal group than to a vascular bed, their reporting authors [21,22] suggested that they are probably not directly caused by cerebrovascular disease or by the defective ventilation of sleep apnea but rather by highly increased sensory afferent 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 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, and some physicians further speculate that these events may be arrhythmogenic through the dorsal motor nucleus of the vagus nerve.

2. Discussion

2.1. Grounds for controversy

Why did not the improved pulmonary ventilation and subsequently improved gas exchange provided during the CPAP and servoventilation clinical trials help to resolve any ischemic lesions that may have been present both in the heart and in the medulla, thereby tending to normalize interactions between the vagal neural structures and the heart?

CO_2 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 watershed areas like the solitary tract nucleus. In normal physiology, this is demonstrated impressively by the ability of hyperventilation to induce loss of consciousness. In patients with heart failure and sleep apnea, arterial carbon dioxide may not seem adequately 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. One can speculate that 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. In the case of the solitary tract nucleus, this would include regulation of heart rate, rhythmicity, and contractility through its efferent output pathway via the dorsal motor nucleus of the vagus nerve.

Evidence of this insidious influence of changing carbon dioxide levels may be seen in the somewhat different results obtained from the two clinical trials [2,8] using different forms of respiratory therapy. In the CPAP trial [8], the patients' airways were simply maintained in a more open position, allowing improved ventilation entirely through the patients' own breathing efforts. In the servoventilation trial, airway maintenance was achieved together with mechanical inspiratory assistance. In the servoventilation 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, there was no net change in the incidence of sudden death compared to the control group. In contrast, the servoventilation trial was stopped when more patients in the study group were dying compared to the control group. Intended to improve oxygenation and gas exchange in ischemic myocardial tissue, it is possible that servoventilation may have paradoxically and perversely worsened circulation in ischemic medullary brain tissue which is probably just as important in causing sudden death, and where the damaging effects of decreased CO_2 levels seem to outweigh any beneficial effects of indirectly increased oxygenation.

In 2017, Hofmann et al. [23] reported some potentially corroborating information from another clinical trial. Oxygen administration for patients with acute myocardial infarction was shown to be unhelpful as a routine therapy in the absence of specific laboratory data in an individual patient showing hypoxemia. This trial conclusion may have some general relevance to heart failure where myocardial ischemia or infarction sometimes plays a role — as either an etiology or a complication. And although patients in the CPAP and adaptive-servo trials did not necessarily receive supplemental oxygen, it was probably presumed by many observers that myocardial oxygenation would be indirectly improved by normalized ventilation and that this would affect outcomes favorably. To such observers, the two sleep apnea trials [2,8] may have revealed that myocardial oxygenation was not generally as critical a parameter in patient management as was carbon dioxide in the brain.

2.2. Gaining ground

Notwithstanding the results of recent trials of respiratory therapy [2,8,23], Shen et al. [24] recently reported that, from 1995 to 2014, the rate of sudden death in heart failure patients actually declined substantially — apparently due to the gradual introduction of medications controlling such circulatory factors as blood pressure, cardiac rate, and myocardial contractility [24]. This meta-analysis of a dozen clinical trials, overlapping each other over 2 decades, offers hope that additional improvements can be made in the future — and it may offer some general direction in how best to approach future therapy.

Why is the risk of sudden death in heart failure patients, frequently with ischemic cardiac disease and sleep apnea, reduced by circulatory improvement but not by ventilatory improvement when deficiencies in both areas seem clearly to be contributors to sudden death? It is conceivable that the answer may lie in the largely unrecognized role of the solitary tract nucleus of the brain medulla, which seems to develop its own ischemic lesions due to afferent neurotoxic input through the vagus nerve in the context of either ischemic cardiac disease or sleep apnea [21,22]. Medications which improve blood circulation influence the brain in largely the same manner that they influence the rest of the body. But respiratory therapy, which directly improves gas exchange in the heart and lungs, collides with counter-current mechanisms in the brain, which results in decreased blood flow. Improvements in systemic circulation [24] (and probably medullary brain circulation) seemed to reduce the risk of sudden death in heart failure patients where respiratory therapy did not [2,8]. Once thought to involve only a tiny subset of neurology patients [9–15], sudden death related to tiny medullary brain lesions may possibly involve a large segment of the general medical population — much of which is not typically considered to have neurological disease.

A thorny lingering subset in the mystery of unexpected sudden deaths are athletes who are considered healthy, only to drop dead during a

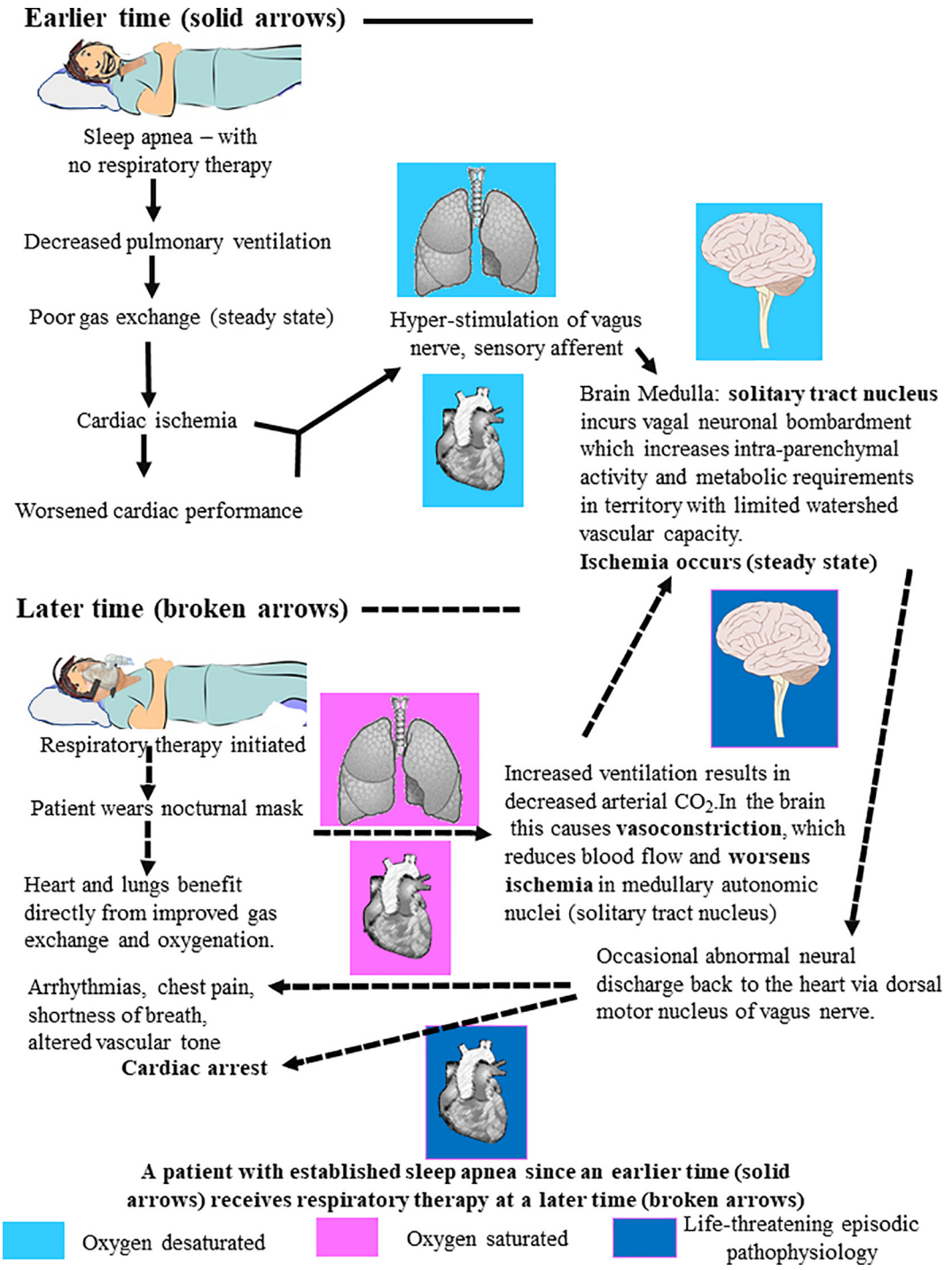

Fig. 1. Diagram of the relationship between the treated and untreated sleep apnea. A patient with established sleep apnea since an earlier time (solid arrows) receives respiratory therapy at a later time (broken arrows).

competitive sporting event [25]. The clinicopathological common denominator in all of these sudden deaths could be exercise-induced tachycardia which may occasionally cause transient ischemia of the heart and solitary tract nucleus, not readily apparent at general autopsy.

2.3. Common ground

It is interesting that several years prior to the publication of any of these clinical trial results [2,8,23–25], the American Heart Association revised its guidelines for cardiopulmonary resuscitation (CPR) outside of a hospital setting — to minimize mouth-to-mouth ventilation and become "hands-only CPR," focusing largely on manual chest compressions.

Patients experiencing cardiac arrest are physiologically compromised in a manner similar to that of patients with heart failure and sleep apnea — only to a much more severe degree. Blood circulation through the heart, lungs, and brain has essentially stopped. The solitary tract nucleus is severely ischemic, yet its capacity for blood flow is preserved to a large extent by the vasodilation in the brain associated with dramatically increased carbon dioxide levels.

The challenge of resuscitation efforts is to improve circulation and oxygenation in all vital organs while blood flow in the brain (and in the solitary tract nucleus) experiences a response to carbon dioxide levels which runs counter-current to that of the other organs. Four clinical trials published from 2000 to 2015 [26–29] have shown no difference in clinical outcomes between patients receiving the more easily administered hands-only CPR and those receiving both chest compressions and mouth-to-mouth ventilation — possibly showing again that the detrimental effects of CO_2-related vasoconstriction in the medulla neutralize or outweigh the beneficial effects of improved myocardial oxygenation. In 2017, the American Heart Association published findings from a nationwide database of out-of-hospital resuscitations in Japan between 2007 and 2012 to confirm its recommendation for hands-only CPR initiated in 2010 [30].

We observed from recent clinical trials [2,8,24] that in managing patients with heart failure and sleep apnea, just as in managing patients with acute cardiac arrest outside of a hospital setting [26–29], the approach that has actually worked to improve patient outcomes is maximizing circulatory assistance and minimizing respiratory assistance.

Fig. 1 shows the relationship between treated and untreated sleep apnea. A patient with established sleep apnea since an earlier time (solid arrows) receives respiratory therapy at a later time (broken arrows).

We believe that all of the relevant clinical trials and analyses reported in the *New England Journal of Medicine* [2,8,23–29] were fundamentally sound in their design, methodology, and execution and that the results were fundamentally correct. But how can this odd and disparate stratification of data be definitively reconciled unto itself? The topic remains wide open [31].

3. Conclusions

In this paper, we conclude that the findings of several clinical trials recently reported in the *New England Journal of Medicine* [2,8,23–29], taken together with neuropathology case studies reported elsewhere [21,22], suggest that additional research is warranted in regard to the mechanisms by which focal medullary autonomic brain ischemia may be related to sudden death in general medical illnesses — and how it may additionally be influenced by changes in arterial CO_2 levels.

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