# Case Reports

## Buspirone Treatment for Apneustic Breathing in Brain Stem Infarct

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**We report a case of brainstem infarction resulting in apneustic breathing, which was alleviated with buspirone. We discuss apneusis, review the literature, and speculate about the benefit of serotonin 1A receptor agonists in the treatment of apneusis and other respiratory disorders.** *Key words: buspirone, mechanical ventilation, apneusis, apneustic breathing.* [Respir Care 2003;48(10):956–958. © 2003 Daedalus Enterprises]

### Case Summary

A 61-year-old man with a history of atrial fibrillation, mitral valve replacement, and previous cerebrovascular accident that resulted in mild left hemiparesis presented to the emergency department with recent onset of shortness of breath and decreased level of consciousness. The patient was responsive to verbal stimuli and had spontaneous opening of the eyes. Using his fingers, he was able to count and add. He had mild hemiparesis on the left side but good motor power on the right side. The patient had no extraocular muscle movement to doll's head maneuver, and the pupils were fixed with a dilated left and constricted right pupil. The chest radiograph was clear, cardiac enzymes were normal, and electrocardiograph revealed low-rate atrial fibrillation. Computed tomography of the brain showed an old right temporal infarct. Magnetic resonance imaging could not be done because of the prosthetic mitral valve. Because of his deteriorating respiratory status, the patient was intubated, started on heparin, and admitted to the intensive care unit, with an original diagnosis of right-sided acute brain stem infarction.

He became stable in the intensive care unit, and subsequently ventilatory support was weaned to low-level synchronized intermittent mandatory ventilation at 6 breaths/min. There were very few apneustic breaths during low-level synchronized intermittent mandatory ventilation, but apneustic breaths became very frequent and apparent during a trial of continuous positive airway pressure. The apneustic breaths were characterized by prolonged inspiratory time and a pause at the end of inspiration, followed by expiration suggestive of apneustic breathing.

Extubation was not feasible in the intensive care unit, so a tracheostomy was performed and the patient was transferred to the respiratory care unit, where he received mechanical ventilation for approximately 2 months. Daily attempts were made to discontinue mechanical support, but to no avail because of consistent episodes of apneusis. Buspirone, previously reported to alleviate apneustic breathing in humans (see Discussion below) was tried as a last resort (10 mg, 3 times a day) after obtaining consent from the family. Three days before the initiation of buspirone therapy and throughout the treatment period, the frequency of apneustic episodes was determined daily with a computerized pulmonary mechanics monitor system ($CO_2$SMO Plus!; Novametrix Medical Systems, Wallingford, Connecticut) that incorporates an adult flow sensor placed between the tracheostomy tube and the Y-piece of the breathing circuit. At the end of each day (ie, after 24 h of data collection) we counted the number of breaths during which inspiratory time lasted more than 15 seconds. Following the administration of buspirone, there was an immediate and marked decrease in the frequency of apneusis (Fig. 1), and on the 6th day of buspirone treatment the patient was off mechanical ventilation and could successfully maintain spontaneous breathing with adequate gas exchange. No evidence of apneusis was noted again.

### Discussion

Apneusis, or apneustic breathing, is an abnormal breathing pattern characterized by a prolonged pause at full in-

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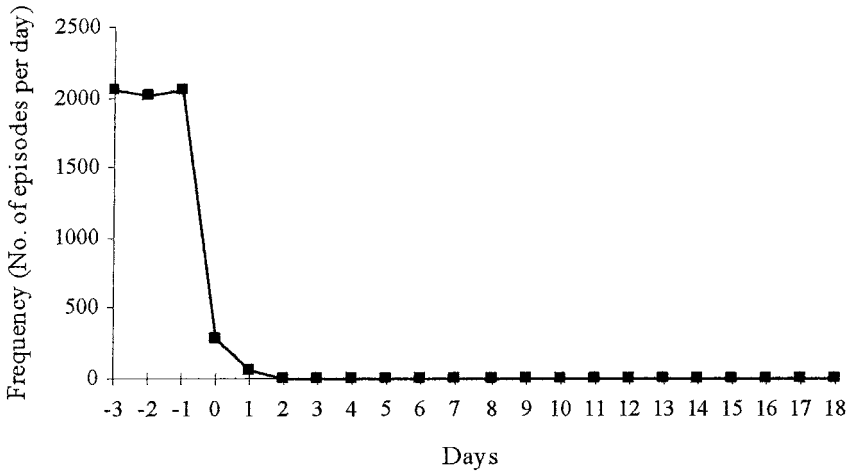


Fig. 1. Frequency of apneustic breathing episodes at baseline and during treatment with buspirone, which was initiated at Day 0. Apneusis was defined as an inspiratory time > 15 seconds.

spiration.[1] Two pontine centers are reported to be involved in the termination of inspiration: the apneustic center and the pneumotaxic center.[2] The transition from inspiration to expiration is regulated by suppression of the apneustic center by inputs from the pneumotaxic center.[2] N-methyl-D-aspartate (NMDA) receptors in the pneumotaxic center, believed to be located in the medial parabrachial and Kölliker-Fuse nuclei in the pontine tegmentum, seem to be involved in the termination of inspiration.[3] In vagotomized animals, lesions in the parabrachial and Kölliker-Fuse nuclei evoke apneusis.[4] "Switching-off " neurons in the medulla oblongata are thought to inhibit the excitatory network of inspiration.[3] One discrete area in the dorsomedial medulla, designated as the dorsal respiratory group, corresponds to the ventrolateral nucleus of the solitary tract in rats.[5] This area has been extensively studied in animals. Blockade of NMDA receptors results in apneusis.[5–7] Vagal inputs upon lung inflation (the Hering-Breuer reflex) suppress apneusis by synapsing with the medullary "switch-off" respiratory neurons.[3,8]

In a recent review by Hilaire and Pasaro[9] the neural mechanisms for respiratory rhythmogenesis in mammals were highlighted in humans (adults and neonates) and animals. They raised doubt as to whether apneustic breathing really occurs in species other than the cat. They further indicated that apneusis is only evident in anesthetized and vagotomized cats. Apneusis is not frequently reported in humans, most probably because the term "apnea" is used to describe most breathing abnormalities. Apneusis has been reported in asphyxiated children,[3,10,11] children with brain stem compression due to achondroplasia,[8] and patients with pontomedullary cardiovascular accidents and tumors.[1,3]

There are no reports that accurately define apneusis with regard to its duration or amount of respiratory effort. Berger et al, in their study of NMDA receptor antagonism and apneusis, included apneustic episodes with inspiratory pauses of 15–80 seconds,[6] so we defined an apneustic episode as an inspiratory pause of > 15 seconds.

The serotonergic system, especially the 5-hydroxytryptamine$_{1A}$ (5-HT$_{1A}$) receptor, has been implicated in the control of respiratory function. Lalley et al found that 5-HT$_{1A}$ agonists, 8-hydroxy-2-(di-*n*-propylamine) tetralin (8-OH-DPAT), and buspirone counteract apneusis in anesthetized cats, including those with apneusis triggered by NMDA receptor agonist MK-801. They suggested that 5-HT$_{1A}$ agonists act on early inspiratory neurons and inhibit their sustained discharge in apneusis.[12]

Wilken et al reported a case of a 2-year-old girl with apneusis (following a brain tumor excision) that resolved with buspirone treatment.[10] Saito et al reported a 6-year-old girl with asphyxia that resulted in brain stem damage and apneusis. Her respiratory status was alleviated with trandospirone, a 5-HT$_{1A}$ agonist available in Japan.[3]

Our patient showed marked improvement in respiratory function with buspirone. Whether the patient improved on his own as a natural course of his brain stem infarct, or because of buspirone cannot be confirmed, but given that several attempts to remove the patient from mechanical ventilation had failed over the course of 2 months and apneusis episodes decreased with buspirone, we think it likely that buspirone affected the course of the patient's illness. The efficacy of buspirone could have been confirmed by the re-appearance of apneustic breathing upon temporary withdrawal of the drug, but this could not be done, for ethical reasons.

In conclusion, apneusis is still not well studied in humans, and its treatment with 5-HT$_{1A}$ agonist seems to be a promising therapy for patients who have suffered cardiovascular accidents or brainstem injuries that affect respiratory function.

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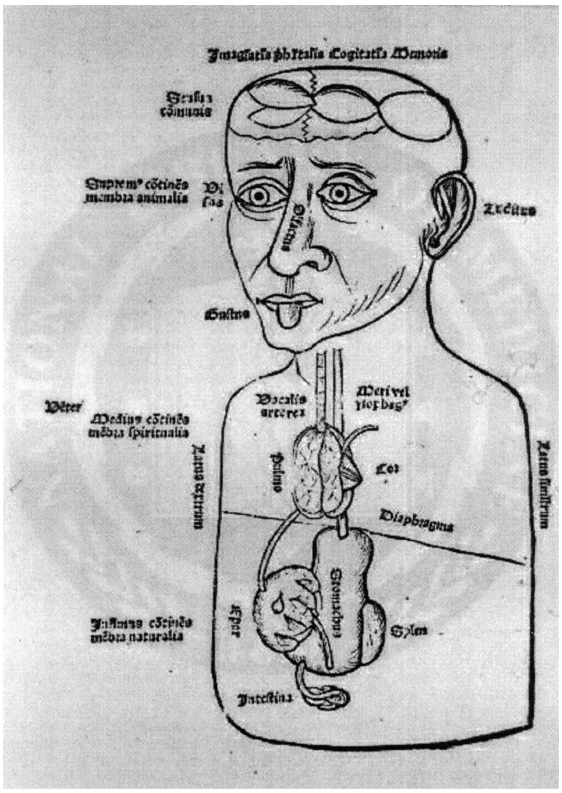


Human figure, half-length, with some of the abdominal internal organs, the senses, and sections of the brain identified.
From Johannes Peyligk, Mechior Lotter,
*Compendium philosophiae naturalis*. Leipzig: 12 Sept, 1499.
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