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REVISED VERSION

Title:

Pathological breathing patterns after pneumococcal rhombencephalitis.

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Conflict of Interest:

The authors report no significant conflict of interest.

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Introduction:

Apneustic breathing is an abnormal breathing pattern characterized by a prolonged inspiratory time with an end-inspiratory pause versus a shorter expiratory time[1]. The termination of respiration is considered to be controlled by the pontine respiratory group. The apneustic breathing pattern is very rare in humans. Patients with failure of autonomic breathing have an impaired autonomic control of ventilation, while their voluntary control remains intact[2]. This is usually due to congenital central hypoventilation syndrome. In rare cases, it can be observed following brainstem lesions. Because of the very rare descriptions of these pathological breathing patterns, still little is known about the impact of specific brainstem lesions on the control of ventilation in humans.

We present a case of a patient with an incomplete locked-in syndrome and a respiratory drive dysfunction consisting of the combination of an apneustic-like breathing pattern while awake and a failure of autonomic breathing during sleep due to the uncommon cause of a pneumococcal rhombencephalitis.

Case Summary:

Two years ago this 15-year-old girl was diagnosed with pneumococcal rhombencephalitis. The diagnosis was made based on a positive polymerase chain reaction for streptococcus pneumoniae on cerebrospinal fluid and on typical abnormalities of the cranial computed tomography (narrow basal cisterns in the fossa posterior and a blurred delineation of the brain stem). After 3 weeks and several weaning trials it became evident that she remained ventilator-dependent and a tracheostomy was placed. She could be discharged 3 months after initial presentation on nearly continuous tracheal ventilation in pressure assist-controlled mode. At the time of evaluation, she is quadriplegic except for some left hand mobility.

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A recent neurological investigation in the Coma Science Group of Liège, Belgium (department of professor S. Laureys), revealed the following data on magnetic resonance imaging (MRI): cerebellar damage and severe brainstem atrophy, most prominent in the medulla oblongata, with areas of chronic gliosis with Wallerian degeneration at the level of the pons and medulla oblongata (fig 1). Although Positron Emission Tomography (PET) also revealed large hypometabolic regions in the cortex, standardized cognitive testing revealed no cognitive dysfunction. She was diagnosed with an incomplete locked-in syndrome with atypical additional supratentorial lesions.

The girl is nearly full-time ventilated by tracheal ventilation. However, she is able to remain free from the ventilator for a maximum of 2 hours when someone is talking to her. The patient was referred to our department for implantation of a phrenic nerve pacing system in order to increase ventilator-free breathing. A series of respiratory tests were performed and prior to each test the patient and her father, who was always present, were informed about the test and agreed with the procedure.

We first performed a phrenic nerve conduction study according to the method described by MacLean and co-workers[3]. This study showed a normal conductance with an asymmetrical diaphragmatic compound muscle action potential. Fluoroscopy of the diaphragm during stimulation showed adequate movement of the diaphragm, although less pronounced on the left side. This unilateral mild reduction in muscle action potential clearly did not explain her ventilator dependency.

For this reason, we performed further investigation. We switched off the tracheal ventilation during daytime while the patient was fully awake, which revealed a deep and slow breathing pattern at a rate of 8 times per minute with apneustic characteristics (fig 2). Over a period of approximately 1 hour, an increase in cardiac rate (from 75 to 85 bpm) was observed. We do not have arterial blood gas data of the patient, but a validated transcutaneous carbon dioxide monitor (Tosca 500)[4] showed an elevation of transcutaneous P_{CO2} (P_{tcCO2}) (from 38 to 45 mmHg)(fig 3). The figure shows that

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oxygen saturation is relatively low even though the patient is ventilated. This is due to mucus accumulation and frequent need for aspiration.

When the ventilator was switched off during slow wave sleep, the patient failed to breathe at all although she was not overventilated (fig 4). After 20 seconds oxygen desaturation occurred and because of severe hypoxia we restarted the ventilator after 38 seconds.

Discussion:

This case shows that an infectious rhombencephalitis with visible lesions at different levels of the brainstem can cause a combination of pathological breathing patterns. This patient shows a respiratory drive dysfunction with an apneustic-like breathing pattern with intermittent oxygen desaturations and an increase of P_{tcCO2} while awake and failure of autonomic breathing during sleep.

The term rhombencephalitis is used to describe encephalitis involving the brainstem and/or cerebellum. Pneumococcal infection is a very rare cause of rhombencephalitis with only a few cases previously reported[5].

Patients with locked-in syndrome are quadriplegic and have anarthria with preserved consciousness and respiratory, cardiac and vasomotor functions. Locked-in syndrome is caused by destructive bilateral brainstem lesions, affecting the corticospinal, corticopontine and corticobulbar tracts. The most common causes are ischemic stroke and hemorrhage[6,7]. Other causes include trauma[7], pontine abscess[8] and brainstem tumors[9]. Our patient suffers from an incomplete locked-in syndrome, with preservation of voluntary breathing and some left hand movement and mouth opening. MRI in this patient confirms lesions in the medullary pyramids and the pons (fig 1), responsible for the locked-in status and the described disorders. To our knowledge, this is the first case of an (incomplete) locked-in syndrome due to pneumococcal rhombencephalitis. Moreover, due to a broader lesion of the

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lateral tegmentum of the pons, this patient has a failure of autonomic breathing, which is not typical for locked-in syndrome.

Control of breathing in humans is complex and has not yet been fully understood. It is not our goal to discuss this in full detail, but we give a short overview. In normal subjects, respiration is controlled by respiratory centers in the brainstem[10]. These respiratory centers receive input from central respiratory pacer cells, central and peripheral chemoreceptors, mechanoreceptors, the midbrain and volitional pathways (=voluntary respiration[11]). Three brainstem areas are considered important: the pontine respiratory group (PRG) or pneumotaxic center in the pons, and the ventral (VRG) and dorsal (DRG) respiratory group in the medulla. The PRG contains inspiratory, expiratory and phase-spanning neurons and is involved in the modification and fine control of the respiratory rhythm. The VRG is the generator of the respiratory rhythm, while the DRG is the primary rhythmic respiratory drive to phrenic motorneurons.

Brainstem lesions may cause characteristic abnormalities in breathing pattern. In animals, apneustic breathing is produced by pontine section. This type of breathing consists of a prolonged inspiratory time with an end-inspiratory pause versus a shorter expiratory time and is very rare in humans[1]. Our patient has an apneustic-like breathing pattern while awake, with a deep and prolonged inspiration, a relative longer inspiration time versus a shorter expiration time, but without obvious end-inspiratory pauses (fig 2). This breathing pattern resulted in exhaustion, with an increase of P_{tcCO2} and cardiac rate after a short time of switching off the ventilator (fig 3). On MRI chronic gliosis with Wallerian degeneration at the level of the pons could be seen (fig 1), probably responsible for this apneustic-like breathing pattern.

Failure of autonomic breathing is caused by destruction of the lateral medulla affecting the VRG, its connections with the DRG, and the fibers crossing over in the reticulospinal tract. This is mainly caused by both bilateral and unilateral medullary infarctions or by bulbar poliomyelitis[2]. In our patient, MRI revealed chronic gliosis with Wallerian degeneration at the level of the medulla

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oblongata (fig 1) as a consequence of pneumococcal rhombencephalitis which could explain the central origin of the apnea. To our knowledge, this is the first description of failure of autonomic breathing caused by a pneumococcal rhombencephalitis.

Because the apneustic-like breathing pattern resulted in exhaustion and an increase of P_{tcCO2} after a short time of switching off the ventilator, implantation of a phrenic nerve pacing (PNP) system was proposed. PNP can improve ventilation and eliminate the need for continuous positive pressure ventilatory support in selected patients with respiratory insufficiency due to injury or disease of the central nervous system. It increases ventilator free breathing and reduces costs. Restoring negative pressure ventilation also improves olfaction. Possible complications of this treatment are related to the surgery (local infection and pulmonary complications following thoracic surgery) or to the pacing system (technical malfunction or injury to the phrenic nerve).[12] Because of her incurable locked-in status, the patient renounced this therapy.

Teaching points:

- Pneumococcal infection can involve the brainstem and/or cerebellum, causing rhombencephalitis.
- Failure to wean a patient from the ventilator is not always a problem of respiratory muscle weakness. Persistent brainstem damage should be considered in the differential diagnosis.
- Pneumococcal rhombencephalitis can cause incomplete locked-in syndrome, as well as brainstem lesions with specific pathological breathing patterns.
- The pneumotaxic center in the pons is involved in respiratory rhythm control. Brainstem lesions at the level of the pons create an apneustic-like breathing pattern with a deep and prolonged inspiration.
- The medulla contains the ventral and dorsal respiratory group. Destruction of the lateral medulla causes a failure of autonomic breathing.

- In patients with impaired breathing due to a central nervous system lesion, phrenic nerve pacing could be considered as a treatment option to improve ventilator free breathing.

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Figure Legends:

Fig 1: Cerebellar damage and brainstem atrophy with areas of chronic gliosis with Wallerian degeneration at the level of the pons and medulla oblongata. Fig 1A: Sagittal T2-weighted MRI image. Large arrow: pons; small arrow: medulla oblongata. Fig 1B: Axial T2-weighted MRI image, arrow: medulla oblongata.

Fig 2: Breathing pattern while awake. Fig 2A: Polysomnography extract of 30 seconds while the patient is awake and ventilated. Respiration frequency 18 per minute, inspiratory time (Ti) 1.4 seconds, total respiration time (Ttot) 3.4 seconds; as set on the pressure controlled mode of the ventilator. Fig 2B: Extract of 30 seconds while the patient is awake and not ventilated. Respiration frequency 8 per minute, Ti 6.8 seconds, Ttot 8.2 seconds; representation of the apneustic-like breathing pattern. VTH = movement of thorax, VAB = movement of abdomen, S_{tcO2} = transcutaneous oxygen saturation, P_{tcCO2} = transcutaneous carbon dioxide pressure.

Fig 3: Measurement of transcutaneous oxygen saturation (S_{tcO2}), transcutaneous carbon dioxide pressure (P_{tcCO2}) and cardiac rate while the patient is awake and the ventilator is switched off, during 1 hour. S_{tcO2} remains stable. P_{tcCO2} raises from 38 to 45 mmHg. Cardiac rate increases from 75 to 85 beats per minute.

Fig 4: Breathing pattern while asleep. Polysomnography extract of 2 minutes while the patient is in deep (slow wave) sleep. On the ventilator in assisted pressure controlled mode, the timed frequency was abruptly diminished from 18 per minute to 1 per minute for a duration of 38 seconds. Although not overventilated (S_{tcO2} 91% and P_{tcCO2} 41 mmHg), the patient fails to breathe autonomously while asleep and S_{tcO2} decreases to 81%. P_{tcCO2} remains stable due to the longer averaging time (50

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seconds) of P_{tcCO2} measurement. VTH = movement of thorax, VAB = movement of abdomen, S_{tcO2} = transcutaneous oxygen saturation, P_{tcCO2} = transcutaneous carbon dioxide pressure.

Key words:

Respiration

Pulmonary ventilation

Neurology

Infection

Locked-in syndrome

Sleep-disordered breathing

Phrenic nerve pacing

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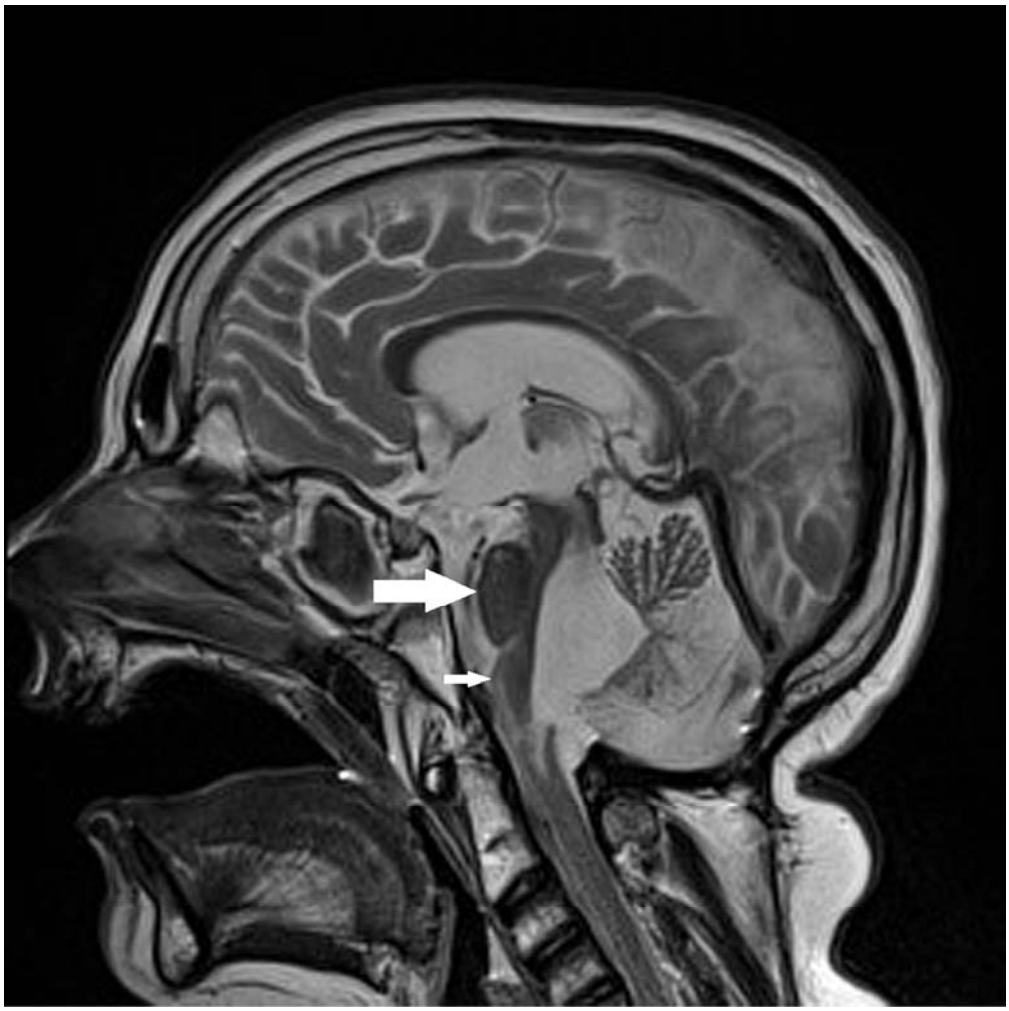

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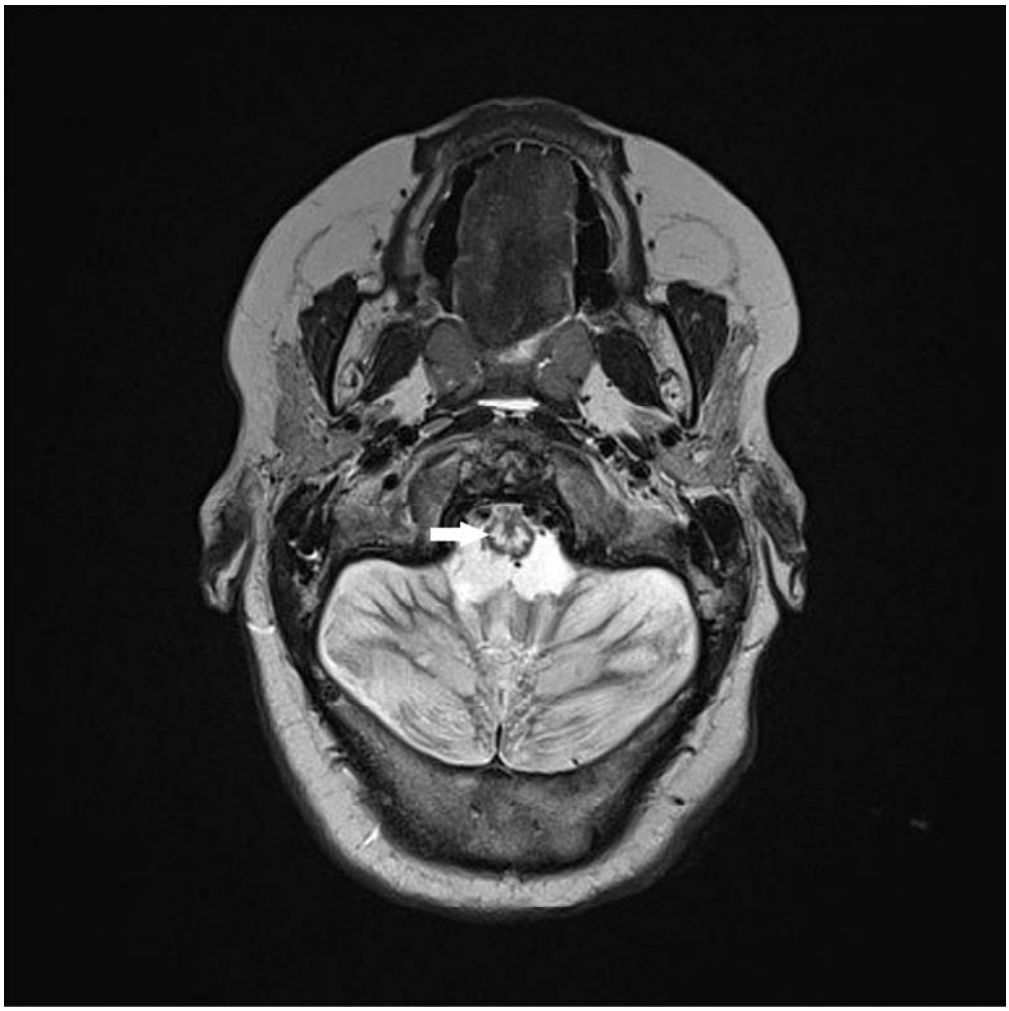

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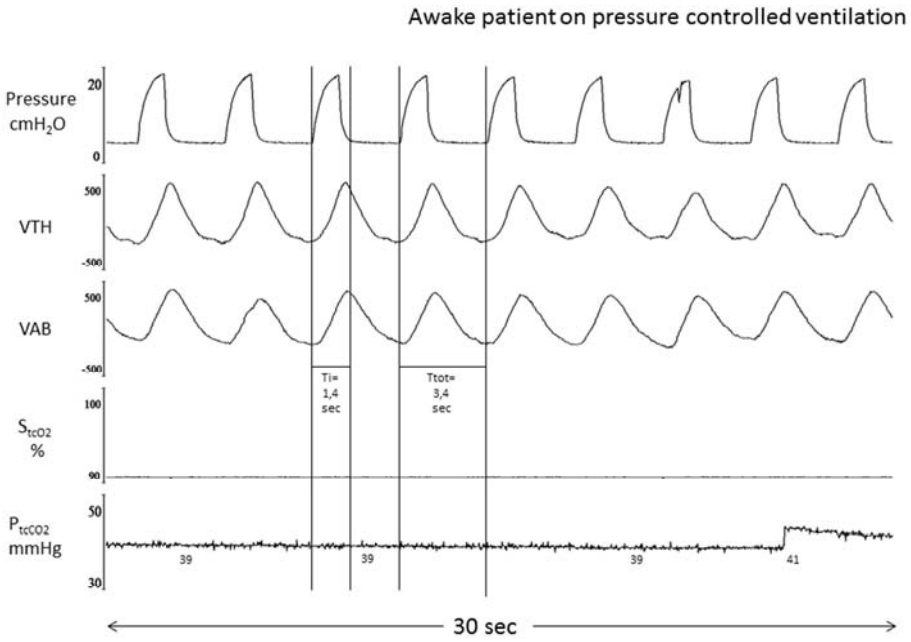

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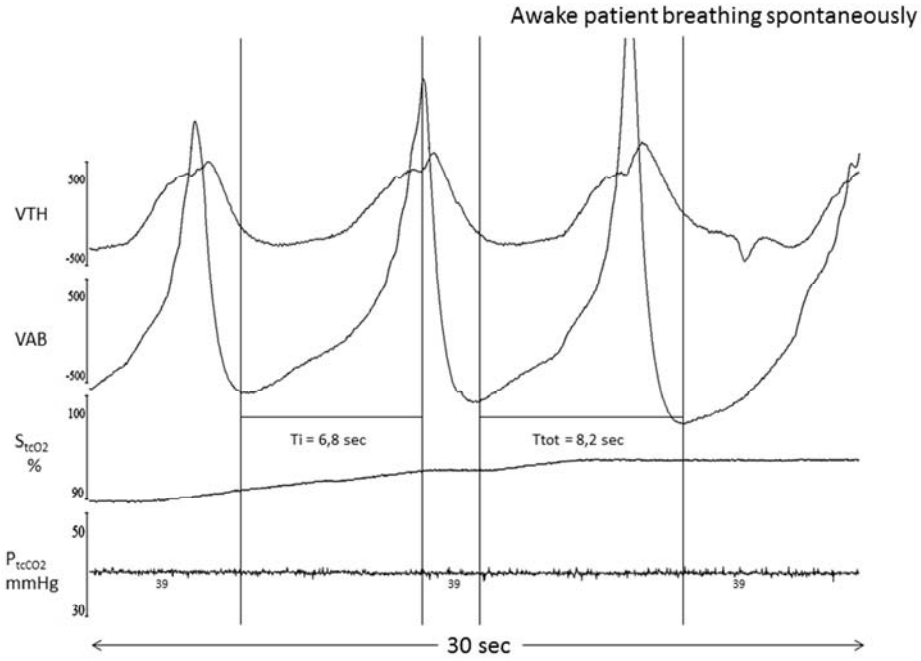

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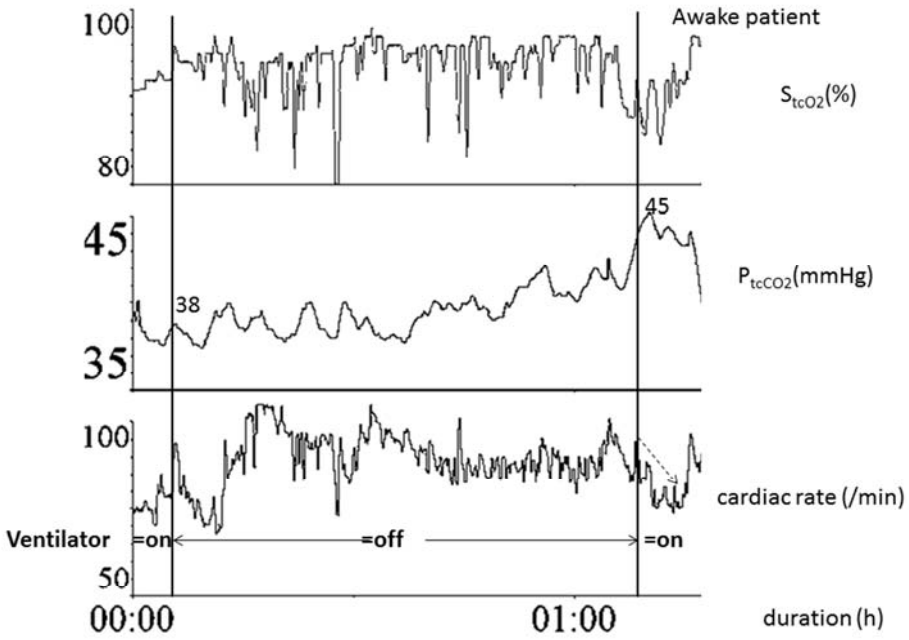

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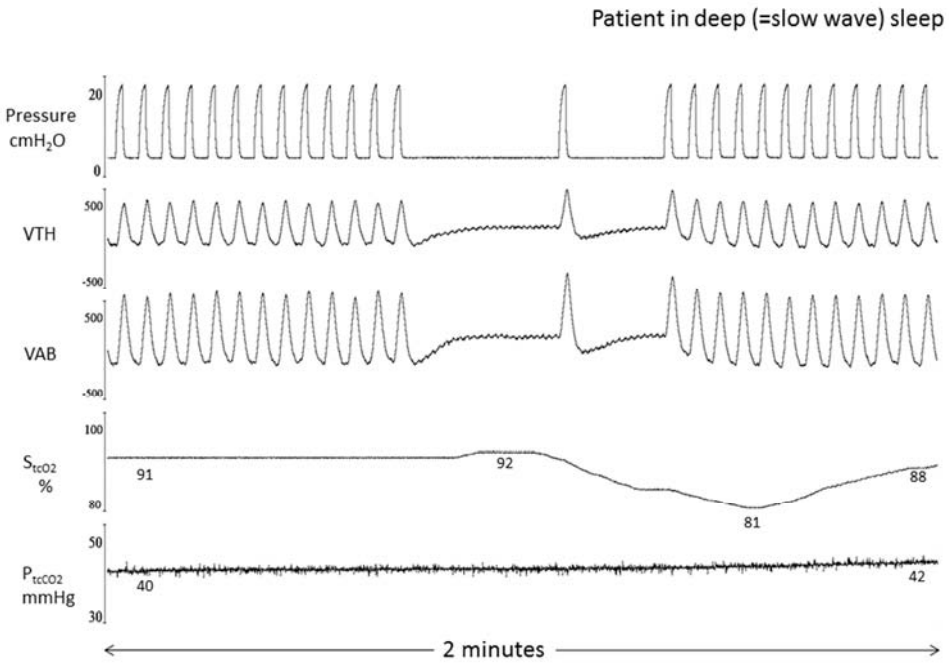

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