Quick guide

Sighing

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What is a sigh? A sigh is a long, deep breath that is often viewed as an expression of stress, sadness, exhaustion or relief. However, the most frequent sighs are unnoticed and occur spontaneously every several minutes, about a dozen times per hour. A sigh is defined as a variant breath type that has two to five times the volume of a normal breath. A typical sigh has a bimodal inspiration in which the first inspiration is indistinguishable from a normal breath (eupnea) followed by a second larger inspiration (Figure 1). This morphology appears as a breath taken on top of a preceding breath. A sigh is often followed by a respiratory pause called a post-sigh apnea.

Producing a sigh is a behavior evolutionarily conserved across mammalian species. Sigh activity starts in fetus as the sigh-like breathing movement, and continues throughout life. Frequent sighing (about 50 per hour) is observed on the first day of postnatal life, which gradually declines to about 20 per hour within the first year.

How was sighing identified? The original description of sighing was made by the famous respiratory physiologist J.S. Haldane in 1919. In his studies on the respiration changes that occur when one lies flat, in particular shallow breathing known as orthopnea, he noticed unique large breaths, now known as sighs. The increased frequency of these large breaths in the lying flat position stimulated him to propose that the purpose of the sigh is to expand the lung, which was continually collapsing as a result of the forced shallow breathing. Thirty years later, McCutcheon characterized the rate of spontaneous sighing in many animals, including mouse, rat, cat, dog and human, and noted that the frequency is inversely proportional to size; like Haldane, he proposed that this was due to the propensity of smaller sized lungs to collapse. These original descriptions inspired subsequent respiratory physiologists who designed rigorous experiments to ascertain the physiological function for sighing.

What is the function of spontaneous sighing? The lung is composed of hundreds of millions of alveoli, the gas exchange units at terminal ends of the respiratory tract, each of which is about 200 micrometers in diameter. During normal breathing, alveoli spontaneously collapse, a pathological condition known as atelectasis. A sigh is hypothesized to reverse any alveolar collapse, because it is a large breath that re-expands all alveoli, filling them all with air. Indeed, normal breathing without sighing results in impaired pulmonary function, measured by increased lung resistance and decreased lung compliance, and ultimately inadequate gas exchange. Consistent with this notion, a sigh can restore the lung resistance and compliance back to normal levels. Additionally, artificial airway occlusion, which causes atelectasis, induces sighing. These sighs, which occur normally every several minutes, are considered as physiological sighs.

How are physiological sighs generated? A physiological sigh is generated in a brainstem region containing a cluster of several thousand neurons called the preBötzinger Complex (preBötC), where the normal inspiratory rhythm is generated. When explanted from the brain (*in vitro*), the preBötC maintains rhythmic respiratory activity and produces activity patterns that reflect not only normal breaths, but also sighs. Within the preBötC, a small subset of neurons (~200 neurons) that express the receptors of the bombesin neuropeptide family are both necessary and sufficient for sighing. These neurons receive bombesin peptidergic signals— neuromedin B (NMB) and gastrin releasing peptide (GRP) — from other breathing control neurons, together forming the central control neural circuit for sighing. Importantly, activation of the preBötC neurons expressing NMB and GRP receptors has been shown to transform normal breaths into sighs, whereas their ablation eliminates sighing. This newly identified peptidergic control circuit strongly supports the central generation of sighing.

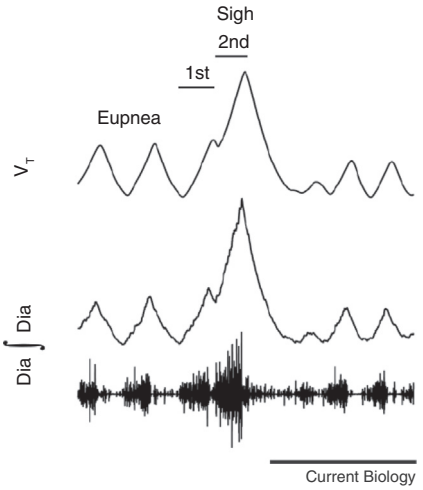

Figure 1. A typical sigh in a breathing activity trace.
A sigh has a bimodal inspiration (1st and 2nd), in which the first inspiration (1st) is indistinguishable from a normal breath (eupnea) in both tidal volume and respiratory muscle activity. V_T, tidal volume; ∫Dia, integrated diaphragm activity; Dia, raw diaphragm activity trace. Scale bar, 1 second. (Modified from Li *et al*., 2016.)

How is physiological sigh regulated by peripheral sensation? Although sighing is generated in the brainstem, and the peripheral signals are dispensable in that the recipients of heart-lung transplants who no longer transmit pulmonary sensory signals to the brain still sigh spontaneously, peripheral sensation does play an important role in regulating sighing. Consistent with the notion that physiological sighing prevents the collapse of alveoli, the reoccurrence of spontaneous sighs is modulated by two kinds of peripheral receptors: mechanoreceptor and chemoreceptor, sensing atelectasis and pulmonary gas exchange, respectively. The pulmonary mechanoreceptors sense the change in lung volume and transmural pressure, and communicate the signals of alveolar collapse to the brain through the vagal nerve. When a spontaneous sigh occurs, the rapidly adapting stretch receptors, a subset of pulmonary mechanoreceptors in the vagal nerve, become intensively activated, indicating an important role of this peripheral receptor

in triggering sighs. In addition to mechanostimuli, hypoxia sensed by the peripheral chemoreceptors, such as the carotid body, also increases sigh frequency. During alveoli collapse, the efficiency of pulmonary gas exchange decreases, and the hypoxic blood shunted through the unventilated pulmonary areas circulates to and activates the chemoreceptors, which reinforces the pulmonary sigh-inducing signal to the brain. The rate of physiological sighs is thus regulated by an integrated signal of mechanosensation and chemosensation that modulates the central sigh control circuit.

Is sighing critical for life? If sighing is so important for preventing atelectasis, is it critical for life? Every day there are thousands of patients in critical care requiring mechanical ventilation to sustain their breathing. In these patients, alveolar collapse is observed when their ventilation is set at a constant tidal volume and breathing frequency. To combat this, sighs are included in the ventilation program every several minutes, resulting in the improvement of both lung compliance and blood oxygen levels. This suggests a critical role of sighing for life. Similarly, we recently were also able to completely eliminate sighing from normal breathing in rodents by ablating the central sigh control circuit: several days after removing sighs, their breathing became irregular, confirming a true necessity for sighing.

How is sighing linked to emotion? There are many ways, beyond language, that we communicate our feelings. We use physical expressions, such as hand or facial gestures, and non-verbal vocalizations, such as laughter, cries, and sighs, to express many different emotions. Interestingly, regardless of cultural differences, many expressions carry the same meanings cross-culturally. Sighing is used to express our feelings of sadness, frustration, stress, or surprise, spanning the full spectrum of emotions. For example, one of the most common uses of a sigh is to express that one is 'giving up', a negative feeling, yet sighs are also used to express positive emotions, like relief. These expressions are likely hard-wired, because people with different language backgrounds can communicate relief just with the sound of sighing, and deaf individuals can express relief to others with just a sigh.

Surprisingly perhaps, emotional sighing is also conserved in other mammals. For example, when rodents are trained to associate auditory tone with an electric tail shock and a light with the omission of the shock, they sigh more when the omission signal is played during the shock signal, which is interpreted as a sigh of relief. If sighing is a key motor behavior of particular emotions that is conserved in model research animals, it provides an important gateway into understanding how emotional sighs, and therefore emotions, are generated.

Are there other functions of sighing? In addition to physiological and emotional sighs, sighs are frequently observed during the transition from sleep to awake. During the arousal of an infant, sighing is the first behavior observed in a series of stereotypic motor activities. Interestingly, the brain electrical activity that indicates arousal occurs immediately after or during most sighs, suggesting that sighing may play an important role in triggering the arousal process.

How does dysregulated sighing affect us? The pathological condition with excessive sighing is called sighing dyspnea, also known as hyperventilation syndrome. This condition was originally characterized in the 1930s in patients complaining of 'shortness of breath'. The most notable change in the breathing pattern of these patients was excessive sighing. Nowadays, sighing dyspnea is a key diagnostic hallmark in anxiety disorders like panic disorder, phobias and post-traumatic stress disorder. Although the etiology of sighing dyspnea is still unclear, it is certainly associated with psychological stress. It will be important to determine if the psychological changes are a consequence of excessive sighing, or whether sighing dyspnea is a symptom of psychological stress.

Sighing is also affected in diseases that impair the breathing control neural circuits. For example, Rett syndrome is a progressive neurological disorder with some of the hallmark features being excessive sighing, breath-holding, hyperventilation, and hand wringing. Increased sighing frequency and altered breathing have also been described in a mouse model of Rett syndrome, which can be rescued by restoring the mutated gene in the brainstem breathing control center, confirming that the excessive sighing is due to dysregulation of the sighing central control circuit. Like sighing dyspnea, however, the pathophysiology of excessive sighing in Rett syndrome is still unknown.

As the full molecular and cellular control of sighing continues to be identified, we can envision being able to harness this understanding to develop pharmacological approaches for controlling sighing. This will provide the ability to properly regulate sighing when it is excessive in psychiatric diseases or to stimulate it in patients who are hypoventilating in the intensive care unit. The birth of this precise pharmacological control of breathing will pave the way for transforming respiratory care medicine.

Where can I find out more?

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