WCHP Respiratory Physiology 2009-2010
CONTROL OF VENTILATION

Clinical rationale and overall goal:

Disorders of respiratory control often decrease alveolar ventilation and therefore may be life-threatening. The overall goal of this classroom discussion is to provide the student with an understanding of central and peripheral mechanisms involved in the regulation of ventilation by oxygen and carbon dioxide and the contribution of alveolar hypoventilation to arterial hypoxemia and hypercapnia.

Sources of information:

The sources of information that will be sufficient for the individual student to master the specific objectives listed below include the following:

- The required text: Guyton & Hall, *Textbook of Medical Physiology, 11th edition*, Chap. 41;
- Handouts, reprints or other Supplementary materials provided by department faculty;
- Lecture notes;

Nota bene: Students are expected to be prepared for class by having read the relevant sections in the text(s) prior to the classroom sessions on individual topics, to take their own notes during classroom sessions, to participate actively in any large-group or break-out group activities, and to try all online quizzes. Students are encouraged to contact the instructor via email (jnorton@une.edu) with any questions. Students are strongly discouraged from using class notes provided by a note service as the sole or even the primary source of information in this course.

Learning objectives:

Following study of the required reading in the assigned texts (or similar sections in other texts available to the student) and attendance at the lectures and/or discussions on this topic, the student should be able to meet the following learning objectives:

1. Define or otherwise indicate an understanding of the following words or phrases: medullary respiratory center; dorsal respiratory group (DRG); ventral respiratory group (VRG); pneumotaxic center (a.k.a., pontine respiratory group, PRG); apneustic center; central chemoreceptor area; carotid body; aortic bodies; apnea; dyspnea; respiratory arrest; respiratory failure; hyperventilation; hypoventilation; inspiratory ramp; pulmonary stretch receptors; pulmonary irritant receptors; pulmonary "j" receptors.

2. Recognize the anatomical locations of the peripheral and central chemoreceptors;

3. Identify the chemoreceptor responsible for the largest ventilatory response to *acute* changes in arterial PCO_2, and describe the role of readjustments in cerebrospinal fluid hydrogen ion concentration in the ventilatory response to *chronic hypercapnia*;

4. Recognize the various areas within the medulla and pons that are thought to be responsible for the generation of a rhythmic pattern of breathing;

5. Recognize the most likely roles of oxygen and carbon dioxide in the regulation of ventilation in each of the following situations:
    a. A normal human subject at sea level at rest;
    b. A normal human subject who lives in Leadville, CO (10,250 ft);
    c. A patient with long-standing chronic obstructive pulmonary disease;
    d. A normal human subject at sea level during exercise;

Regulation of ventilation – two problems

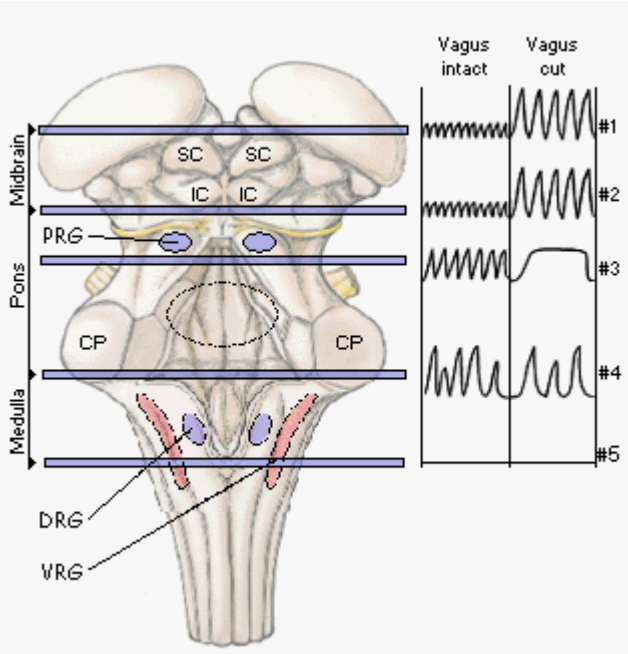
The regulation of ventilation involves two distinct, but related, tasks. The first is *genesis of the respiratory rhythm*, consisting of repeated cycles of inspiration and expiration, accomplished by a central pattern generator (CPG). The second is *regulation of the overall level of ventilation* to assure normal levels of arterial PO_2 and PCO_2 in the presence of changes in metabolic demand, posture, and mechanical conditions or during non-ventilatory behaviors such as vocalization and eating.

The following discussion is only an attempt to provide the student with a framework for understanding and integrating facts and concepts related to the control of ventilation, and *the information in this handout is not meant to substitute for attendance in class or completion of the assigned reading in the required textbook*.

Genesis of the Respiratory Rhythm

A classic method for determining the location of neuronal centers such as the respiratory CPG is to transect the neural axis at various levels and observe the results. Such observations were made as early as the second century by Galen, who was the physician for gladiators in the Greek city of Pergamon. He observed that a sword strike to the upper cervical spine caused breathing to stop, leading to rapid death. In contrast, a sword blow to the lower cervical spine caused paralysis, but breathing persisted. He reproduced these lesions in animals and correctly concluded that the brain was necessary for breathing and that it sends information *via* the spinal cord to the diaphragm.

The figure below is a diagrammatic representation of the midbrain, pons, and medulla that illustrates the effects of transection at different levels on ventilatory activity. Identified anatomical landmarks indicated on the surface of the structures are the superior colliculus (SC), inferior colliculus (IC), and cerebellar peduncles (CP). The thick horizontal blue lines represents the transections, labeled on the far right as #1-#5. The two columns of tracings at the right of the diagram represent patterns of ventilatory activity produced by the transections, either with the vagal afferents intact ("vagus intact") or without vagal afferent inputs ("vagus cut"). The exercise of working through the effects of transection is useful in identifying the various components of the respiratory center and their functions in establishing or modifying the basic respiratory rhythm.



Removal of the cerebral cortex and cerebellum (transection #1) or elimination of the midbrain (transection #2) have little effect on ventilatory pattern. With transactions at these levels, cutting the vagi and thereby eliminating vagal afferent input decreases ventilatory frequency and increases tidal volume. This indicates the general nature of the influence on ventilatory patterns of vagal afferent inputs entering below the midbrain level. If the transection occurs in the upper pons (#3), frequency falls and tidal volume increases. Eliminating vagal afferents in this instance produces an *apneustic* ventilatory pattern – long inspiratory efforts punctuated by brief expiratory gasps.

Transection between the pons and the medulla (#4) causes an irregular but still spontaneous breathing pattern, which is essentially unaffected by cutting the vagus nerves. A transection at the lower border of the medulla (#5) results in apnea.

The results of transection studies such as those described above support the existence of neuronal pools in the medullary portion of the brain stem that serve as a CPG capable of initiating and maintaining an irregular inspiratory and expiratory pattern. These neuronal pools are designated as the **dorsal respiratory group** (**DRG**) and the **ventral respiratory group** (**VRG**). The dorsal respiratory group (DRG) contains primarily inspiratory neurons and is located in and around the *nucleus tractus solitarius* (NTS). One of the major functions of the DRG is to integrate sensory information from the peripheral chemoreceptors *via* the glossopharyngeal (CN IX) and vagus (CN X) nerves, as well as from respiratory-related receptors in the lungs and thorax. The ventral respiratory group (VRG) contains both inspiratory and expiratory neurons. The VRG is much longer than the DRG, and the rostral end (also known as the Botzinger complex) and caudal ends of the VRG are expiratory, with the intermediate region primarily inspiratory. Despite the detailed anatomical knowledge of the medullary respiratory centers, the question of exactly where the respiratory CPG is located and how the basic respiratory rhythm is generated remains unanswered.

The lower two-thirds of the pons appears to encourage inspiration, and is designated as the **apneustic center**; the upper one-third of the pons, called the **pneumotaxic center** (or **pontine respiratory group, PRG**), produces periodic inhibition of the apneustic center and/or the DRG. The pneumotaxic center and the apneustic center appear to modulate the basic respiratory pattern but are not essential in generating it, with the pneumotaxic center and its vagal afferents serving as an "off-switch" for inspiration. The role of the apneustic center in the normal regulation of ventilation in humans is unknown.

Regulation of the Overall Level of Ventilation

The overall level of ventilation, expressed typically as minute ventilation, or $\dot{V}_E$, is determined by the sum of various types of afferent information arriving in the pons and medulla. The table below provides a summary of the various types of receptors, their locations, their afferent pathways, the stimulus(i) to which they respond, and the ventilatory response.

RECEPTOR	LOCATION	AFFERENT PATHWAY	STIMULUS	VENTILATORY RESPONSE
Peripheral Chemoreceptors	Carotid bodies Aortic bodies	Carotid sinus nerve Vagus nerve	↓ PaO_2, ↑ $PaCO_2$, ↓ Arterial pH (rapid)	↑ Minute ventilation ↑ Alveolar ventilation
Central Chemoreceptors	Superficial ventrolateral Medulla	?	↑ $PaCO_2$ ↓ Arterial pH (slow),	↑ Minute ventilation ↑ Alveolar ventilation
Pulmonary Stretch Receptors	Airway smooth muscle	Vagus	Lung inflation	Hering-Breuer reflex Inspiratory inhibition
Irritant Receptors	Between airway epithelial cells	Vagus	Noxious gases Foreign particles Cold air Histamine	Hyperpnea Bronchoconstriction (asthma) Coughing
Type "J" receptors	Walls of pulmonary capillaries	Vagus	Pulmonary congestion Pulmonary edema	Rapid, shallow ventilatory pattern
Thoracic stretch receptors	Intercostal muscles	Spinal afferents	Muscle stretch	Coordination of ventilatory muscle activity
Pain receptors	Throughout body	Spinal afferents	Noxious stimuli	↑ Minute ventilation

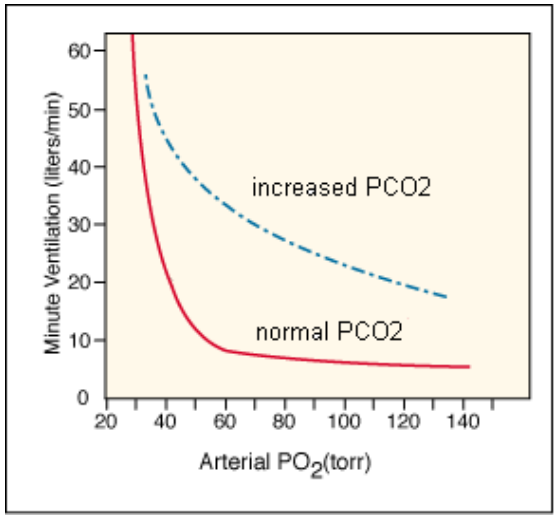
Chemoreceptor control of ventilation

The respiratory system attempts to regulate the arterial levels of oxygen, carbon dioxide, and hydrogen ion. This is accomplished by two sets of chemoreceptors – peripheral and central. Hypoxia, hypercapnia, and acidosis (decreased pH) all cause an increase in ventilation, which tends to raise arterial PO_2, decrease arterial PCO_2, and decrease hydrogen ion concentration (increase pH).

Peripheral chemoreceptors

The peripheral chemoreceptors are primarily responsible for the ventilatory response to decreased arterial PO_2. Increased PCO_2 and hydrogen ion concentration also stimulate these receptors, but to a lesser extent, and serve to make the peripheral chemoreceptors more sensitive to hypoxemia. Peripheral chemoreceptors exist in two locations – the *carotid bodies*, located at the bifurcation of the internal and external carotid arteries, and the *aortic bodies*, scattered along the underside of the aortic arch. (The carotid bodies should not be confused with the carotid sinuses, the arterial baroreceptor located at the origin of the internal carotid artery.)

The figure below illustrates the ventilatory response to changes in arterial PO_2 mediated by the peripheral chemoreceptors, under conditions of a fixed, normal PCO_2 (solid line) and a fixed, increased PCO_2 (dashed line).



The ventilatory response to decreasing PO_2 at a fixed normal PCO_2 (the solid curve, starting from 150 mm Hg in the figure) is relatively small until the PO_2 falls below about 60 mm Hg. Further decreases in PO_2 below this level cause dramatic increases in ventilation. The change in the slope of the O_2 response curve occurs at an arterial PO_2 that represents the "shoulder" of the ODC. An arterial PO_2 of 60 mm Hg corresponds to an arterial percent saturation of about 90%, and below this level of PO_2 oxygen content begins to decrease significantly. If arterial PCO_2 is increased, the ventilatory response to decreasing PO_2 at a fixed, increased PCO_2 (dashed curve above) is greater at every level of arterial PO_2.

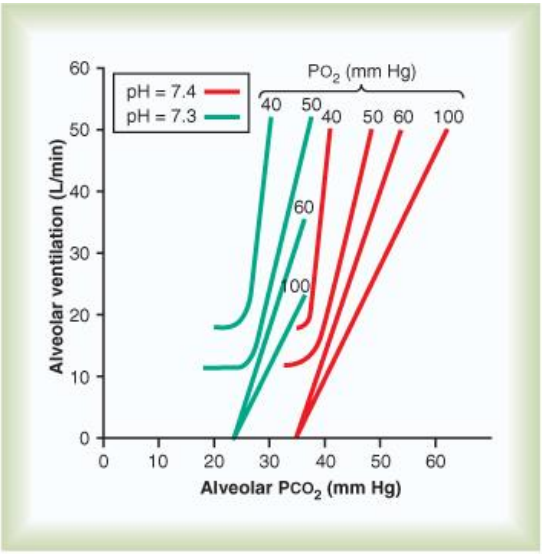
The chemosensitive cells in the carotid and aortic bodies are the glomus cells, roughly spherical cells with a number of neuron-like characteristics. The glomus cell response to decreased PO_2, increased PCO_2, and decreased pH involves an inhibition of potassium channels, leading to glomus cell depolarization, opening of voltage-gated calcium channels, secretion of neurotransmitters (including acetylcholine, dopamine, norepinephrine), and stimulation of nearby afferent nerve fibers. The mechanism by which potassium conductance is affected is different for the three stimuli, but the final common pathway is the same – depolarization and transmitter release.

The peripheral chemoreceptors respond quickly to the changes described above. These chemoreceptors are among the most highly perfused tissues in the body, receiving a blood flow that is many times the amount necessary to satisfy the metabolic needs of the cells comprising the chemoreceptors. Because of the high level of perfusion, the partial pressures of oxygen and carbon dioxide, and the hydrogen ion concentration, in the tissue of the peripheral chemoreceptors is essentially that of the arterial blood.

Central chemoreceptors

In a healthy, normal human subject, the central chemoreceptors are the primary source of information regarding the effectiveness of ventilation. The neurons in the central chemoreceptor regions, located near the surface of the ventrolateral medulla and in other nuclei in the brainstem, appear to respond primarily to arterial hypercapnia, although the actual parameter sensed is an increase in local hydrogen ion concentration within the brain caused by increased PCO_2. The central chemoreceptors appear to be located at a site that responds to changes in the PCO_2 of the arterial blood and the cerebrospinal fluid (CSF). Since the protein concentration of brain extracellular fluid (ECF) and cerebrospinal fluid is less than that of normal plasma, the change in hydrogen ion caused by changes in PCO_2 in these regions is enhanced.

The figure below, taken from the required text, shows the ventilatory response to *acute* changes in alveolar (and, therefore, arterial) PCO_2. This is a very complicated figure, but one that contains important information, so a full explanation is warranted. Each of the eight individual curves in the figure below represents a relationship between alveolar/arterial PCO_2 and alveolar ventilation in L/min, as mediated by the central chemoreceptors. The steep slope of each of the individual curves indicates that the ventilatory response to changes in PCO_2 is pronounced, with ventilation almost doubling with a change in PCO_2 from 40 to 45 mm Hg. These changes in ventilation are the result of changes in PCO_2 and therefore hydrogen ion concentration, in the vicinity of the central chemoreceptors.



Input from the peripheral chemoreceptors can modify the central chemoreceptor response. The eight curves in the figure above are divided into two sets, one set obtained at a normal arterial pH of 7.40 (four curves on the right), and the other at an acidic pH of 7.30 (four curves on the left). Comparison of the two sets of curves at different pH values shows that moving from a normal pH to an acidic pH causes the CO_2 response curves to shift to the left on the PCO_2 axis. This means that *the ventilatory response increased PCO_2 is enhanced by increased blood hydrogen ion concentration*, as the result of increasing afferent input from the peripheral chemoreceptors. In addition, at each level of arterial pH, the ventilatory responses to changes in PCO_2 were obtained at four different levels of arterial PO_2 – 40, 50, 60, and 100 mm Hg. At a given level of arterial pH, *the central chemoreceptor response to increased PCO_2 is enhanced by decreased arterial PO_2* and increased afferent input from the peripheral chemoreceptors, as indicated by the increasing slope of the CO_2 response curves as PO_2 falls.

Chronic hypercapnia and the accompanying respiratory acidosis is associated with a gradual attenuation of the ventilatory response over days, due to increased hydrogen ion excretion by the kidney and an increase in the bicarbonate concentrations in both the brain ECF and the CSF. Return of the hydrogen ion concentration in the vicinity of the central chemoreceptors toward normal reduces the signal responsible for the increase in ventilation. This may be important clinically, since in patients with chronic respiratory disease, arterial hypoxemia, and hypercapnia secondary to CO_2 retention, the primary ventilatory drive may come the hypoxemia sensed by the peripheral chemoreceptors. The over-zealous administration of oxygen to such patients may remove this hypoxic drive for ventilation,

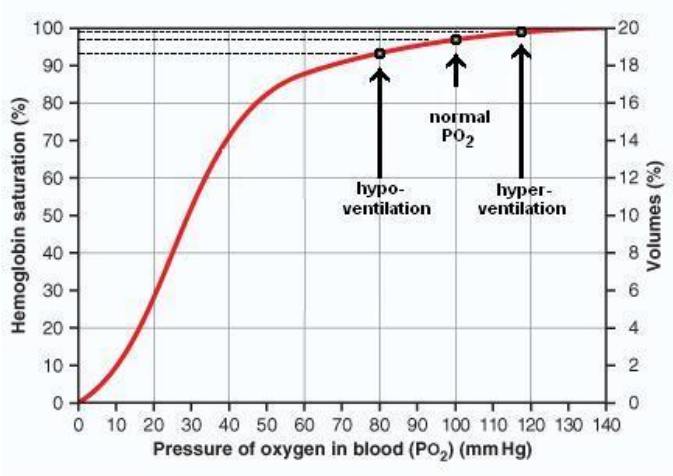
resulting in a decrease in alveolar ventilation and a rapid rise in PCO_2 to levels that may cause what is term "CO_2 narcosis" and death from hypoventilation.

The reverse is true in chronic hypocapnea, due, for example, to ambient hypoxia associated with altitude. The initial, acute increase in ventilation due to hypoxemia, sensed by the peripheral chemoreceptors, results in a decrease in arterial PCO_2 and a respiratory alkalosis. The subsequent decreases in brain ECF and CSF hydrogen ion concentration partially offset the acute ventilatory response to hypoxia by inhibiting the central chemoreceptors, but as brain and CSF hydrogen ion concentrations are returned toward normal over the next few days, the hypoxic ventilatory response can be fully manifested.

Ventilatory regulation and oxygen transport

The minute-to-minute regulation of ventilation by carbon dioxide and hydrogen ion concentration has surprisingly little effect on oxygen uptake in the lungs and oxygen transport to the tissues. This is due primarily to the differences between the shapes of the carbon dioxide dissociation curve and oxygen dissociation curve (see the respiratory gas transport discussion and handout). Examination of the normal oxygen dissociation curve reveals that arterial oxygen saturation is above 90% over a wide range of arterial PO_2 values from 60 to 600 mm Hg – *i.e.*, the oxygen dissociation curve is relative flat over this range of oxygen partial pressures. The carbon dioxide dissociation curve, in contrast, is relatively steep in the range of normal arterial and venous partial pressures, and changes in PCO_2 dramatically affect CO_2 concentration, bicarbonate concentration, and hydrogen ion concentration. The student should be reminded at this point that increases in alveolar ventilation cause alveolar and arterial PCO_2 to fall, and alveolar and arterial PO_2 to rise. The minute-to-minute increases or decreases in alveolar ventilation that help keep PCO_2 and arterial hydrogen ion concentration within their normal ranges do change arterial PO_2 somewhat, but these changes in PO_2 are not accompanied by substantial alterations of arterial oxygen content.

For example, hyperventilation induced by the onset of a non-respiratory (metabolic) acidosis – *e.g.*, diabetic ketoacidosis – could decrease alveolar and arterial PCO_2 to 25 mm Hg or less. The corresponding alveolar PO_2, calculated using the *alveolar air equation*, would be about 118 mm Hg, enough to increase the percent saturation of pulmonary end-capillary blood from its normal level of 96-97% to 98-99%, not much of a change in percent saturation or oxygen content. This is indicated on the graph below as the point representing "hyperventilation". Conversely, hypoventilation caused by the onset of a non-respiratory (metabolic) alkalosis – *e.g.*, prolonged vomiting and loss of gastric acid – sufficient to increase alveolar and arterial PCO_2 to 55 mm Hg would be accompanied by a decrease in calculated alveolar PO_2 to about 80 mm Hg, still high enough to yield a percent saturation of 93-94% in pulmonary end-capillary blood. This is represented on the graph below as the point representing "hypoventilation". In either case, relatively large changes in alveolar ventilation, PCO_2, and hydrogen ion concentration would be accompanied by very little change in the percent saturation and oxygen content of pulmonary end-capillary blood.



Routine regulation of PCO_2 and hydrogen ion concentration are thereby effectively uncoupled from the regulation of arterial oxygen content unless, of course, arterial PO_2 falls below 60 mm Hg, at which point the peripheral chemoreceptor drive from the hypoxemia becomes physiologically significant. Interestingly, the arterial PO_2 below which hypoxic ventilatory drive becomes important, about 60 mm Hg, is the PO_2 below which arterial oxygen con-

tent will begin to fall significantly. The hypoxic ventilatory drive appears to serve as a protection against arterial desaturation below 90% or so.

Other factors modulating ventilatory activity

In addition to input from the chemoreceptors, the respiratory center receives input from a variety of stretch receptors and irritant receptors, as well as input from higher CNS centers that coordinate respiratory activity with non-respiratory activities, shown in the table presented a few pages back in this handout.

Pulmonary stretch receptors are slowly adapting receptors that sense the stretch of airway walls and thereby provide feedback information about lung volume to the respiratory center. A classic example of how these pulmonary stretch receptors work is the Hering-Breuer reflex, one of the first examples of negative feedback control, first reported in 1868. Lung inflation above that achieved in normal breathing activity inhibits further inspiration, and changes the breathing pattern one with a smaller tidal volume and higher frequency. This may protect the lungs from over-inflation, while preserving adequate levels of alveolar ventilation, or may simply serve as method of minimizing the work of breathing by choosing an optimum combination of frequency and tidal volume.

Irritant receptors are rapidly adapting stretch receptors that are sensitive to a variety of extrinsic chemical stimuli, such as cigarette smoke, and intrinsic chemical stimuli such as prostaglandins and histamine. Their function seems to be to detect airway irritants and adjust the ventilatory pattern to one that would help eliminate them from the respiratory tree.

Juxtacapillary receptors, or *"J" receptors*, are associated with a network of small, non-myelinated, slowly conducting nerve fibers in the walls of the alveoli and conducting airways and respond to a variety of stimuli. Stimulation of these receptors results in bronchoconstriction and a rapid-shallow breathing pattern, causing turbulence within the larger airways that would favor deposition of foreign substances in the mucus lining this part of the respiratory tree. The "J" receptors are thought to be responsible for the dyspnea associated with pulmonary congestion and edema.

Yawning

Yawning is a common physiological event that has been described since antiquity. Yawning is present in all mammals and, in some form, in all vertebrates. Yawning occurs in humans of all ages, even in the fetus as early as the 15^{th} week of gestation. The physiological significance of yawning is hotly debated, with some researchers claiming it has a respiratory purpose, others claiming it modulates attention, and still others think yawning is a form of group communication.

Does yawning have a respiratory purpose? The deep inhalation of yawning and the associated stretching of the limbs presumably increase alveolar ventilation, increase arterial PO_2, decreases arterial PCO_2, and increase venous return into the chest. However, neither breathing pure oxygen or gases high in carbon dioxide has any effect on yawning frequency, suggesting that yawning does not serve a primary respiratory function.

Is yawning an alerting response? Yawning often occurs when we must maintain a high level of vigilance in an environment devoid of stimulation. Yawning induces increased sensory afferent input from the facial nerve distribution that stimulates the brainstem and cortical EEG activity. This theory and the first may actually work together. A decrease in vigilance induces hypoxia and hypercapnia, which stimulates the brainstem reticular formation, inducing yawning. The yawning then increases somatic sensory afferents and blood oxygenation, thereby stimulating brain areas and increasing vigilance.

Is yawning a form of non-verbal communication? During a boring lecture, a student may yawn to maintain alertness, but the yawning may be a signal to the lecturer that he/she is not very interesting. Yawning during a conversation may signal a loss of interest or a refusal to continue further discussion. Yawning may therefore be a non-verbal form of group behavior with high social significance. [1]

[1] Daquin, G, J Micallef, and O Blin. Yawning. *Sleep Medicine Reviews* 5(4):299-312, 2001.

Another explanation of yawning describes it as a way for the body to cool the brain[1]. Volunteers yawned more often in situations in which their brains were likely to be warmer. Researchers took advantage of the well-established tendency of people to yawn when those around them do – the so-called contagious yawn mentioned above. The volunteers were asked to step into a room by themselves and watch a video showing people behaving neutrally, laughing or yawning, with some volunteers asked to breathe only through their noses as they watched and others asked to press warm or cold packs on their foreheads. Observers watching through a one-way mirror counted how many times the volunteers yawned. The two conditions thought to promote brain cooling (nasal breathing and forehead cooling) practically eliminated contagious yawning. The study may also help explain why yawning spreads from person to person. A cooler brain is a clearer brain, so yawning actually appears to be a way for an individual to stay more alert, and contagious yawning may have evolved to help groups remain vigilant against danger.

[1] Gallup, AC, and GG Gallup. Yawning as a Brain Cooling Mechanism: Nasal Breathing and Forehead Cooling Diminish the Incidence of Contagious Yawning. *Evolutionary Psychology* 5(1): 92-101, 2007.