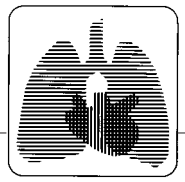

opinions/hypotheses

Respiratory Sinus Arrhythmia*

Why Does the Heartbeat Synchronize With Respiratory Rhythm?

Fumihiko Yasuma, MD, FCCP; and Jun-ichiro Hayano, MD, FCCP

Respiratory sinus arrhythmia (RSA) is heart rate variability in synchrony with respiration, by which the R-R interval on an ECG is shortened during inspiration and prolonged during expiration. Although RSA has been used as an index of cardiac vagal function, it is also a physiologic phenomenon reflecting respiratory-circulatory interactions universally observed among vertebrates. Previous studies have shown that the efficiency of pulmonary gas exchange is improved by RSA, suggesting that RSA may play an active physiologic role. The matched timing of alveolar ventilation and its perfusion with RSA within each respiratory cycle could save energy expenditure by suppressing unnecessary heartbeats during expiration and ineffective ventilation during the ebb of perfusion. Furthermore, evidence has accumulated of a possible dissociation between RSA and vagal control of that heart rate, suggesting differential controls between the respiratory modulation of cardiac vagal outflow and cardiac vagal tone. RSA or heart rate variability in synchrony with respiration is a biological phenomenon, which may have a positive influence on gas exchange at the level of the lung via efficient ventilation/perfusion matching.

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Key words: hypercapnia; hypoxia; pulmonary gas exchange; respiratory-circulatory interactions; respiratory sinus arrhythmia; vagal activity

Abbreviation: RSA = respiratory sinus arrhythmia

The fundamental function of respiration is to maintain homeostasis as an interface between the interior and exterior of the human body. The respiratory system is open to the outside through ventilation via the alveoli, while the circulatory system consists of two closed loops of pulmonary and systemic circulation (Fig 1). The neural network, mainly the autonomic nervous system, is known to play a major role in the interaction of respiration and circulation. For example, the oscillations in sympathetic nerve discharge synchronizing with respiratory rhythm were described by Adrian and colleagues[1] > 70 years ago. However, the mechanisms responsible for the respiratory modulation of autonomic activity remain incompletely understood today. The fluctuations in BP in synchrony with respiration are unlikely to be mediated by sympathetic activity, because the time constant of the sympathetic vasomotor response is too long to respond faithfully to neural signals oscillating at a frequency of > 3 to 4 cycles per minute.[2] Moreover, plenty of mechanical and reflex stimuli are likely to affect respiratory modulation of BP (some with opposing influences on BP). For example, a breathing-related swing in BP seems to depend not only on respiratory rate but also on the fullness of the central circulation, and the direction and magnitude of an intrathoracic pressure change during respiration.[3]

Respiratory sinus arrhythmia (RSA), one of the physiologic interactions between respiration and circulation, is heart rate variability in synchrony with respiration, by which the R-R interval on an ECG is

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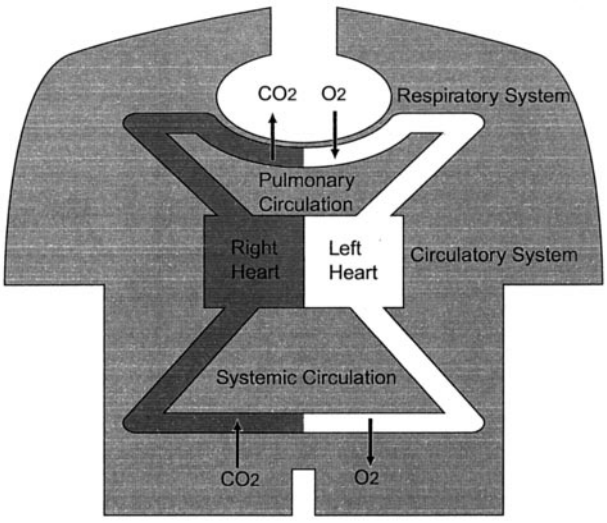

FIGURE 1. Respiratory and circulatory systems. The respiratory system is open to the exterior of the human body through ventilation in the alveoli, while the circulatory system consists of two closed loops of pulmonary and systemic circulation. Pulmonary circulation originates in the right ventricle and terminates in the left atrium. Systemic circulation originates in the left ventricle and terminates in the right atrium.

shortened during inspiration and prolonged during expiration. RSA has been a focus of study since its first description by Ludwig[4] in the mid-19th century. In Figure 2, a polygraphic recording of a conscious dog is displayed, since dogs are known to have a prominent RSA.[5,6] A clustering of heartbeats (R waves of an ECG) during inspiration and a scattering during expiration are clearly seen. Although the significance of RSA had not been fully investigated, we demonstrated in an experimental animal study[7] that the efficacy of pulmonary gas exchange was improved by RSA. The concept that RSA is not simply the secondary product of other known reflexes but that it has its own physiologic role is gaining favor among pulmonary and cardiovascular physiologists nowadays.[8,9] In this review article, the authors briefly address the physiologic role, mechanisms, and clinical significance of RSA, while presenting the recent research on this phenomenon.

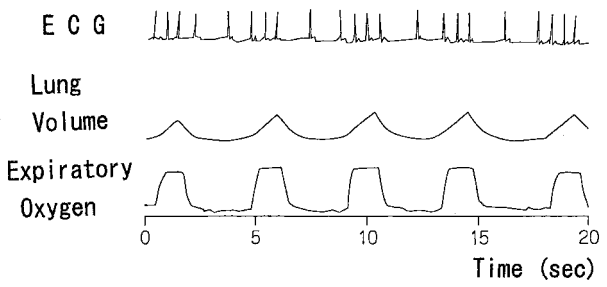

FIGURE 2. A polygraphic recording showing RSA in a conscious dog. Recordings of electrocardiography, lung volume, and airway O_2 tension (arbitrary unit) were displayed. The conscious dog lying quietly breathed via an endotracheal tube inserted through a permanent tracheostomy. A clustering of heartbeats (R waves of electrocardiography) during inspiration and a scattering during expiration are clearly seen.

PULMONARY GAS EXCHANGE AND RSA

In our earlier study,[7] we postulated that "RSA has a function to improve the pulmonary gas exchange, synchronizing the heartbeat with respiratory rhythm." In the representative RSA in a dog, the clustering of heartbeats during inspiration and their scattering during expiration are observed (Fig 2). With RSA, as the instantaneous blood volume circulating in the pulmonary circulation depends on the corresponding heart rate, the relationships between alveolar gas and capillary blood undergoing pulmonary gas exchange during inspiration and expiration are as those shown in Figure 3. At any given moment, approximately 10% of the blood in the whole vasculature is distributed in the pulmonary circulation, and 10% of the blood in the pulmonary circulation is distributed in the pulmonary capillary bed.[10] Hence, the stroke volume is almost equivalent to the bolus of blood momentarily circulating in the pulmonary capillary bed. This indicates that most of the pulmonary capillary blood volume interfacing with the alveolar gas would be replaced with each

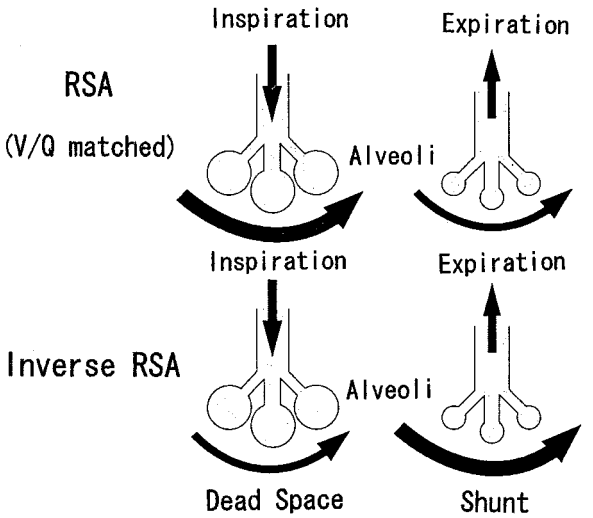

FIGURE 3. Scheme showing the conceptual effects of RSA (*top*) and its inversion (*bottom*) on the relationship between alveolar gas volume and capillary blood flow during inspiration (*left*) and expiration (*right*). Curved horizontal arrows and vertical arrows indicate the volume of blood flow circulating in the pulmonary capillary bed and the direction of alveolar gas interfacing with the pulmonary capillary blood. V/Q = ventilation/perfusion.

heartbeat. Therefore, the distribution of heartbeats within each respiratory cycle could critically affect the efficacy of respiratory gas exchange.

In seven anesthetized dogs that had been prepared with a bilateral cervical vagotomy, an RSA simulation model was created after the elimination of endogenous autonomic activities by means of a reserpine injection.[7] Respiration-linked heartbeat fluctuations were generated by electrical stimulation of the right cervical vagi, whereas negative pressure ventilation was generated by the diaphragm pacing technique (so-called *electrophrenic respiration*) to mimic spontaneous breathing.[11] During inspiration, the phrenic nerve was electrically paced to generate negative intrathoracic pressure, to preserve the physiologic respiratory pump effects on venous return. During expiration, the pressure in the thorax was equal to the atmospheric pressure. Vagal stimulation was performed under the following three conditions: phasic stimulation during expiration (*artificial RSA*; Fig 3, top); inspiration (*inverse RSA*; Fig 3, bottom); and constant stimulation (control) causing the same number of heartbeats per minute as artificial and inverse RSA. We found that artificial RSA decreased both of the ratios of physiologic dead space to tidal volume and physiologic shunt to cardiac output by 10% and 51%, respectively, but increased O_2 uptake by 4% compared with the control. In contrast, we also found that inverse RSA increased the ratios of both physiologic dead space to tidal volume and physiologic shunt to cardiac output by 14% and 64%, respectively, and decreased O_2 uptake by 14% compared with the control. Under these three conditions, the tidal volume, minute ventilation, heart rate, cardiac output, and arterial BP were all unchanged. Our results may well support the hypothesis that RSA improves the pulmonary O_2 uptake (*ie*, the pulmonary gas exchange) by matching perfusion to ventilation within each respiratory cycle, and, hence, suppressing unnecessary heartbeats during expiration and ineffective ventilation during the ebb of perfusion.

Lorenzi-Filho et al[12] found that the fluctuations in ventilation during Cheyne-Stokes respiration could amplify and entrain oscillations in heart rate in the absence of hypoxia or arousal from sleep. Cheyne-Stokes respiration is a form of periodic breathing characterized by a cyclical fluctuation with periods of central apneas alternating with episodes of hyperpnea in a gradual waxing-and-waning fashion. In this particular pattern of periodic breathing, a scattering of heartbeats occurs during the apneic phase, whereas a clustering of heartbeats is observed during the hyperpneic phase. Thus, the periodic oscillation in the heart rate during Cheyne-Stokes respiration is related to respiration and resembles an exaggerated form of RSA, but at a lower frequency of periodic breathing. The entrainment of heart rate oscillations by Cheyne-Stokes respiration is a good example of the synchronization of circulation with respiration within each cycle length of respiratory periodicity. From a clinical standpoint, the conditions of more than half of congestive heart failure patients are complicated by Cheyne-Stokes respiration.[13,14] The teleology of the frequent coexistence of periodic breathing in congestive heart failure is likely to improve the efficacy of pulmonary gas exchange by entraining heartbeats with phasic hyperpnea within each cycle length of Cheyne-Stokes respiration. Hence, this phenomenon may function to save "unnecessary" heartbeats during the apneic phase and presumably to achieve the maximum efficacy of gas exchange in a failing heart.

Chemoreflex and RSA

The response of RSA to hypoxia and hypercapnia provides the physiologic compensation against the turbulence/stressor challenged from outside the organism (Fig 1). RSA is easily influenced by such factors as cardiopulmonary function, pattern of breathing, sleep/wakefulness, anesthesia, body position, age, gender, species, and many other variables. In an RSA investigation, these variables must be strictly controlled. Therefore, the authors used unanesthetized, conscious dogs for this purpose, since the responses of RSA to chemostimulations have not been systematically investigated.[15,16] Moreover, RSA has been well-investigated in canines,[17,18] which have a strong RSA.[5,6]

Each dog was trained to lie down on its side quietly in the laboratory with a tube inserted through a permanent tracheostomy so that respiratory/metabolic parameters could be measured on a breath-by-breath basis. BP was continuously monitored with a surgically implanted telemetry unit in the femoral artery. Electrocardiograms and electroencephalograms also were monitored with subcutaneous needle electrodes. Using electroencephalograms and behavioral criteria, the levels of sleep and wakefulness were assessed, and only the data collected during quiet wakefulness were included in this study.[19] A rebreathing technique was used for the loading of hyperoxic hypercapnia and isocapnic hypoxia. The magnitude of RSA was assessed by a complex demodulation to delineate the time-dependent changes in oscillatory components in the R-R interval on the ECG and in arterial BP.[20,21]

Hypercapnia

The central chemoreceptors, respiratory center, and effector organs serve to maintain $PaCO_2$ within a range of 37 to 43 mm Hg in healthy humans. Representative tracing during acute hyperoxic hypercapnia[15] is shown in Figure 4, *left*. During progressive hypercapnia lasting approximately 3 min, the partial pressure of end-tidal CO_2 increased from 36 to 55 mm Hg, and, concomitantly, the tidal volume and respiratory rate increased from 230 to 850 mL and from 18 to 22 breaths/min, respectively. Both heart rate and BP were unchanged. It is noteworthy that RSA was augmented with hypercapnia.

Vagal stimulation generally decreases both heart rate and cardiac contractility. In this study, while no significant change was noted in heart rate, the magnitude of RSA was intensified. Therefore, it is likely that RSA was exaggerated without any tonic increase in cardiac vagal outflow during central chemostimulation with acute and progressive hypercapnia. This increase in RSA magnitude is thought to result from the direct stimulation of central chemoreceptors by the increased PCO_2. Furthermore, Sasano et al[22] recently demonstrated that the increase in RSA magnitude was observed even when concomitant changes in respiratory rate and tidal volume were eliminated. In the central chemoreflex, as seen in baroreflex,[23] a coupling of RSA and vagal nerve activity disappears and, as a result, a dissociation between heart rate variability and vagal tone occurs. These findings indicate that certain stimuli that do not affect cardiac vagal tone could modify RSA magnitude. Shykoff et al[24] experimentally suggested that RSA was regulated centrally and that its magnitude was proportional to the respiratory drive. When humans are exposed to acute and progressive hypercapnia, expelling CO_2 gas from the lungs is necessary for survival, thus stimulating respiration. Moreover, the pulmonary gas exchange should be accelerated, resulting in an intensified RSA, with which physiologic/functional dead space is reduced by matching perfusion and ventilation within each respiratory cycle.

Hypoxia

The bilateral carotid bodies located in the bifurcation of the internal and external carotid arteries

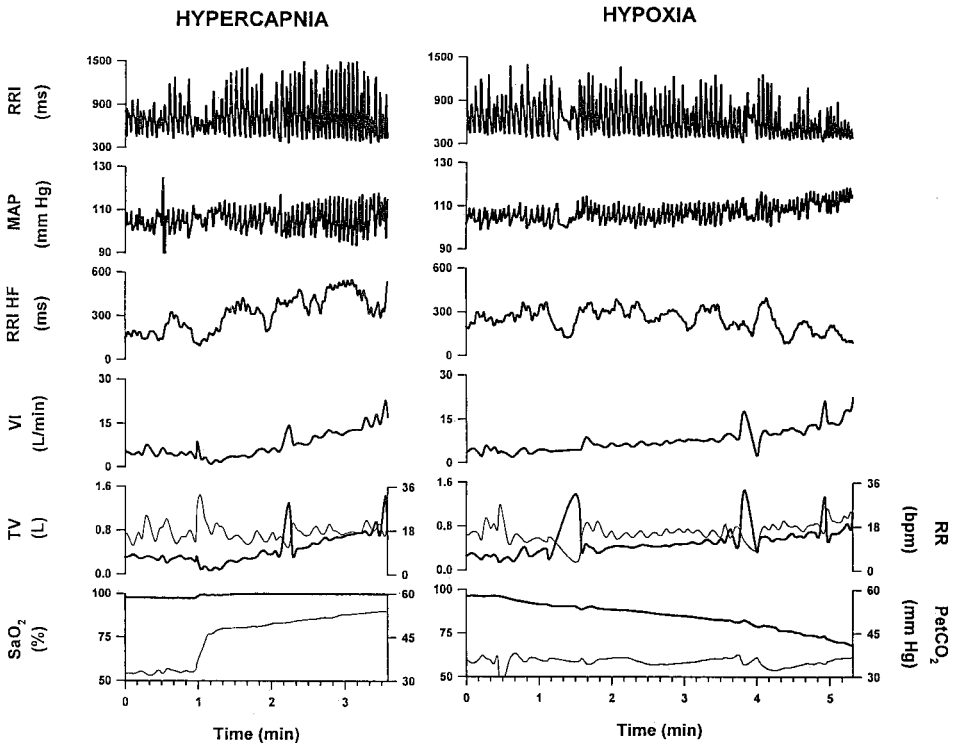

Figure 4. Representative tracings during hyperoxic hypercapnia (*left*) and isocapnic hypoxia (*right*) in a conscious dog. RRI = R-R interval; MAP = mean BP; RRIHF = amplitude of R-R interval oscillation in high-frequency band; VI = minute volume of inspiration; TV = tidal volume; RR = respiratory frequency; Sa_{O_2} = saturation of arterial blood; and $PetCO_2$ = partial pressure of end-tidal CO_2. Note that RSA (the magnitude of respiratory oscillation of RRI and its quantitative reflection in RRIHF) increases with progressive hypercapnia (*left*), whereas it decreases with hypoxia (*right*).

serve primarily as the peripheral chemoreceptor. They sense the arterial Po_2, and that information is transmitted to the respiratory center in the brainstem, which regulates depth and frequency of respiration.

A representative tracing during acute isocapnic hypoxia[16] is shown in Figure 4, *right*. During progressive hypoxia lasting approximately 5 min, O_2 saturation of arterial blood decreased from 95 to 73%, and tidal volume and respiratory rate concomitantly increased from 240 to 800 ml, and from 18 to 24 breaths/min, respectively, while both heart rate and BP were augmented. It is noteworthy that the RSA was attenuated with hypoxia.

These changes may provide compensatory responses against a threat of hypoxemia. When humans are exposed to acute and progressive hypoxia, maintaining oxygenation of the vital organs is necessary for survival. To increase oxygen uptake and transport, both ventilation and cardiac output need to increase. When the relative expiration period shortens with an increasing respiratory rate, alveolar gas is less likely to be saturated. Thus, cardiovascular synchronization within each respiratory cycle would lose its advantage. Moreover, because diastolic cardiac filling is a major limiting factor of cardiac output when the heart rate is elevated, fluctuations in the heart period such as those with RSA would be disadvantageous for increasing cardiac output. A simultaneous surge in BP is convenient for redistribution of the blood flow to the vital organs. The sympathetic nervous system is mainly activated during peripheral chemostimulation with hypoxia, which is supported by data from previous investigations revealing a prompt excretion of catecholamine in anesthetized dogs[25] and increased sympathetic nerve activity of microneurographic technique in conscious humans.[26,27] Sympathetic excitation during hypoxia is suggested by the concomitant increase in both heart rate and BP, as shown in Figure 4, *right*.

Hypercapnia vs Hypoxia

The influences of hypoxia and hypercapnia[28] on the amplitude of RSA at a comparable level of minute ventilation of 15 L/min were significantly different. RSA was attenuated with hypoxia, whereas it was augmented with hypercapnia. According to the concept of permissive hypercapnia in patients with respiratory distress who have been treated with mechanical ventilation, a considerable level of hypercapnia (*ie*, 50 to 70 mm Hg) is permitted as long as their oxygenation is maintained.[29] Therefore, the increase in $Paco_2$ frequently seen in patients with respiratory failure is less of a lethal threat than a decrease in Pao_2.[30,31]

Mechanisms of RSA

Heart rate is determined by the firing frequency of the sinus node of a cardiac pacemaker. This frequency is determined by the balance between the cardiac sympathetic and vagal activities to the sinus node. The activity of the cardiac vagal nerve is assumed to be modulated by respiration, and hence the sinus node activity is secondarily modulated by the respiratory rhythm. Regarding the genesis of RSA, both the respiratory and circulatory centers in the brainstem appear to be responsible. Moreover, projections from the cerebral cortex, limbic system, and other parts of the brain to the brainstem should exist.

In mammals, the following two major mechanisms have been recognized for generating RSA: direct modulation of the cardiac vagal preganglionic neurons by central respiratory drive; and inhibition of cardiac vagal efferent activity by lung inflation.[24,32,33] The cardiac vagal efferent fibers are fired preferentially during expiration, and this respiratory-related activity is maintained even after the vagal nerve is resected at the peripheral to the recording site.[34,35] The vagal efferent fibers are more powerfully excited during expiration by stimulating the arterial chemoreceptors and baroreceptors.[36,37] Respiratory modulation could also be mediated by gating of the excitatory reflex inputs into the preganglionic neurons. Indeed, the membrane potential of cardiac vagal preganglionic neurons has been demonstrated to be hyperpolarized during each inspiration due to the arrival of an acetylcholine-mediated inhibitory postsynaptic potential, which makes neurons less amenable to excitatory inputs during inspiration.[38] On the other hand, afferent activity arising in the lungs is also an important mechanism with which to generate RSA. Lung inflation inhibits cardiac vagal efferent activity and evokes tachycardia by stimulating the pulmonary C-fiber afferents (*ie*, pulmonary stretch receptors). This effect may be so strong that it reverses the bradycardia evoked by arterial chemostimulation into a tachycardia.[39]

The efferent cardiac vagal nerve plays the major role in the genesis of RSA, whereas the contribution of the cardiac sympathetic nerve seems to be minimal. During inspiration, as described above, the activity of the efferent cardiac vagal nerve is almost abolished. Hence, the R-R interval on an ECG is shortened. In contrast, during expiration, the activity of the efferent cardiac vagal nerve reaches its maximum, thus extending the R-R interval. The difference in the R-R interval between inspiration and expiration can be regarded as an indication of the magnitude of RSA, which is assumed to reflect the cardiac vagal outflow within its physiologic range.[40,41]

Accordingly, the magnitude of RSA has been widely used as a clinical measure of cardiac vagal activity.[42] A neural basis for RSA has been demonstrated by its elimination or substantial attenuation following cervical vagotomy,[43] ganglionic blockade,[44] cholinergic blockade,[5] and heart transplantation.[45]

Clinical Significance of RSA

The magnitude of RSA is assessed as the amplitude of the high-frequency component of the fluctuation of the R-R interval (0.15 to 0.80 Hz), utilizing the frequency analysis of heart rate variability on electrocardiography. For an accurate assessment in short-term electrocardiography recording, an examinee's tidal breathing should be standardized due to the frequency-dependent characteristic of RSA.[46,47] When a frequency analysis of heart rate variability is performed with 24-h ambulatory electrocardiography, the clinical use of RSA as a marker of autonomic activity should be limited. In long-term recording with ambulatory electrocardiography, the effects of breathing on the magnitude of RSA must be considered.

RSA is most prominent in infants and is attenuated as humans age.[48] This mechanism may be particularly important during non-rapid eye movement sleep, when high vagal activity and prominent RSA may partially offset the detrimental effects of hypoventilation on gas exchange.[49,50] Within an individual age group, athletes have a stronger RSA than do nonathletes,[51] which also applies to adults who exercise routinely compared to those who do not.[52] In patients with malignant arrhythmia who survive after cardiopulmonary resuscitation, RSA is very much weakened.[53] RSA is attenuated in patients with coronary artery disease, even when they have no history of acute myocardial infarction or congestive heart failure.[54] Moreover, their prognosis is proportionally poor according to the attenuation in RSA, and the number of affected coronary arteries increases as the magnitude of RSA decreases.[55] In diabetic patients, a diminished RSA is the most sensitive marker of autonomic neuropathy.[56]

Summarizing the above findings in the literature, it seems rather clear that the capacity to generate RSA is well-preserved in young and healthy individuals, but is diminished in older individuals with various diseases whose conditions are complicated by cardiovascular diseases, diabetes mellitus, and the like. In this context, RSA represents a "cardiac age" or a "cardio-pulmonary reserve."[48] When deep and slow breathing patterns are obtained through autogenic training, using techniques such as yoga and tai-chi, RSA is secondarily augmented due to its frequency-dependent characteristic.[46] In most cases, mental concentration and/or psychological relaxation occur simultaneously.[57,58] From the teleologic standpoint, RSA avoids unnecessary heartbeats during expiration, providing a physiologic respite for the cardiopulmonary system. The mechanism of the central origin of RSA, the interaction of the respiratory and circulatory centers, and the roles of the cerebral cortex, reticular activating system, limbic system, and other parts of the brain in generating RSA are unknown. Hence, these issues must be the focus of future studies.

Conclusions

Respiratory-circulatory interactions similar to RSA are widely observed in birds, fish, and mammals.[59] In spontaneously breathing ducks, respiration-related oscillations in heart rate, which is similar to RSA in mammals, are observed.[60] In resting fish, gills are ventilated by a pulsatile water flow throughout the respiratory cycle, and the heartbeat occurs in 1:1 synchrony with respiration, resulting in a coincidence of the periods of maximum flow rate of blood and water across the gills.[61] These observations indicate that RSA or heart rate variability in synchrony with respiration is a biological phenomenon, which may have a positive influence on gas exchange at the level of the lung via efficient ventilation/perfusion matching.

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