Hypothesis paper

Hypothesis: respiratory sinus arrhythmia is an intrinsic resting function of cardiopulmonary system

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Abstract

A hypothesis is presented that explains the physiological reasons why the magnitude of respiratory sinus arrhythmia (RSA) appears to correlate with cardiac vagal tone. The hypothesis is that RSA is an intrinsic resting function of the cardiopulmonary system. Although RSA is mediated by respiratory modulation of cardiac vagal outflow and its magnitude is used as an index of cardiac vagal activity, RSA itself reflects cardiorespiratory interaction. RSA is universally observed among vertebrates throughout the evolution, suggesting that it may bear an intrinsic physiological role. Recent studies have shown that RSA improves pulmonary gas exchange efficiency by matching alveolar ventilation and capillary perfusion throughout respiration cycle. This suggests that in resting animals and humans, RSA could save cardiac and respiratory energy by suppressing unnecessary heartbeats during expiration and ineffective ventilation during waning phases of perfusion. Furthermore, evidence is accumulating for possible dissociation between the magnitude of RSA and vagal control of heart rate, suggesting separated and independent regulations for respiratory modulation of cardiac vagal outflow from those for cardiac vagal tone. By our hypothesis, the apparent associations between RSA and cardiac vagal tone are explained as indirect consequences; i.e., whenever the cardiac vagal tone changes in response to the resting level of the cardiopulmonary system, RSA appears to change parallel to it. Our hypothesis seems more consistent with both physiological and clinical evidence about RSA than that presuming RSA is an index of cardiac vagal activity.

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1. Introduction

Heart rate variability (HRV) is referred to as the quantity of physiological spontaneous fluctuations of heart period that correspond to physiological sinus arrhythmias in ECG. Short-term HRV (typically that observed within several minutes of recordings) is used as an index of autonomic function and a large body of evidence supports its validity [2,7,31,51]. Nevertheless, such evidence is mostly phenomenological or observational and there remain fundamental questions to be answered. Those are (1) whether HRV is merely a sum of passive and secondary products of other known reflexes [39,40] or it includes purposely generated fluctuations for own physiological roles and (2) whether the association between HRV and autonomic function is a mere chance or an inevitable consequence of underlying physiology.

It is unknown whether there is a unified answer to these questions; however, evidence is accumulating for that at least a part of HRV component could bear active physiological roles and which seem to explain the association between HRV and autonomic function. One of such

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components is respiratory sinus arrhythmia (RSA) that is quantitatively measured as a high-frequency (HF) component and is widely used as an index of cardiac vagal activity. In this article, we propose a new hypothesis about physiological role of RSA that could explain the fundamental reasons for the association between RSA and cardiac vagal activity.

2. Hypothesis

The hypothesis we propose is that RSA is an intrinsic resting function of the cardiopulmonary system. This hypothesis was developed based on our previous finding that RSA improves pulmonary gas exchange efficiency by matching alveolar ventilation and capillary perfusion throughout respiration cycle. This suggests that in resting animals and humans, RSA could save cardiac and respiratory energy by suppressing unnecessary heartbeats during expiration and ineffective ventilation during waning phases of perfusion. By our hypothesis, the apparent associations between RSA and cardiac vagal activity are explained as the indirect consequences; i.e., they appear to change parallel to each other, whenever they change in response to the resting level of the cardiopulmonary system; but, otherwise, they could dissociate from each other. In the following sections, we review the physiological features of RSA and show the evidence supportive for the hypothesis.

3. Physiological features of RSA

3.1. RSA as a component of short-term HRV

Short-term HRV measured as beat-to-beat variation of R–R interval shows unique behaviors in responses to stress and diseases. In the absence of external or internal turbulence/stressors, most of physiological parameters are kept constant around their own set points and the states in which such constancy is lost are considered as disorders. Following to this concept, R–R interval is expected to be stable at rest and to become unstable under distress or diseases; however, the reverse is the case. As shown in Fig. 1, fluctuations of R–R interval is most strong in healthy subject at rest, it reduces with mental and physical stresses, and is almost disappeared in patients with severe heart failure even at rest. These and other physiological and clinical evidence accumulated so far [2,7,31,51] indicate that fluctuation of R–R interval is a characteristic of healthy peoples at rest and is suppressed in distress and diseases, suggesting that the fluctuation may reflect a purposely generated function but not a passive response to stimuli.

In short-term HRV such as those shown in Fig. 1, RSA is the most prominent and consistent component. RSA is an oscillation of heart period in synchrony with respiration, which appears in power spectrum of R–R interval as a peak within the so-called HF band (0.15–0.45 Hz) or, more appropriately, as a peak at respiratory frequency. It is
believed that RSA is mediated solely by vagus due to the difference in frequency characteristics of signal transfer between sympathetic and vagal modulation of heart rate [4]. Because the magnitude of RSA is attenuating with progressive suppression of cardiac vagal activity and abolished by complete vagal blockage with atropine, RSA has been proposed and widely used as a quantitative index of cardiac vagal function [1,13,19,33], in the respiratory gas exchange. Fig. 2 shows a polygraph has been proposed and widely used as a quantitative index observed in fish [37,45], the most likely roles of RSA exist abolished by atropine, RSA As implied by the cardiorespiratory synchronization progressive suppression of cardiac vagal activity and expiration are clearly seen.

3.2. RSA as a cardiorespiratory interaction

However, RSA itself is a physiological phenomenon reflecting cardiorespiratory interaction, typically, shortening of R–R interval with inspiration and lengthening during expiration. Cardiorespiratory interactions similar to RSA are widely observed over species of vertebrates from water-breathing fishes to mammals and birds [47], indicating a highly conserved biological phenomenon throughout the evolution. In resting fish, gills are ventilated with pulsatile water flow throughout ‘respiratory’ cycle and heartbeat occurs in 1:1 synchrony with the respiration so that it results in coincidence of the periods of maximum flow rate of blood and water at the gills [37,45]. This cardiorespiratory synchronization is mediated by vagus and abolished by atropine [45]. Respiration-related oscillations in heart rate, similar to RSA in mammals, are also observed in spontaneously breathing ducks [6]. These suggest that RSA may bear important intrinsic physiological roles in respiration.

In mammals two major mechanisms have been recognized for generating RSA. These are direct modulation of the cardiac vagal preganglionic neurons by central respiratory drive and inhibition of cardiac vagal efferent activity by lung inflation [11,22,44]. The cardiac vagal efferent fibers fired preferentially during expiration and this respiratory-related activity survives section of the vagus peripheral to the recording site [25,26,29]. The vagal efferent fibers are more powerfully excited during expiration by stimulating the arterial chemoreceptors and baroreceptors [10,28]. Thus, the respiratory modulation could be mediated also by gating of the excitatory reflex inputs into the preganglionic neurons. Indeed, the membrane potential of cardiac vagal preganglionic neurons have been demonstrated to be hyperpolarized during each inspiration due to the arrival of acetylcholine-mediated inhibitory postsynaptic potential, which makes the neurons less amenable to excitatory inputs during inspiration [14]. On the other hand, afferent activity arising in the lung is also important mechanism of RSA [9,34]. Lung inflation inhibits its cardiac vagal efferent activity and evokes a tachycardia through stimulating pulmonary C-fiber afferents. This effect may be so strong that it reverses the bradycardia evoked by arterial chemoreceptor stimulation into a tachycardia [9]. The fact that our body furnishes these sophisticated mechanisms for generating RSA also suggests the presence of active physiological roles.

3.3. RSA and pulmonary gas exchange

As implied by the cardiorespiratory synchronization observed in fish [37,45], the most likely roles of RSA exist in the respiratory gas exchange. Fig. 2 shows a polygraph of electrocardiogram, arterial pressure and lung volume recorded in an unanesthetized, awake, resting dog. The dog is the animal known to have most prominent RSA among mammals [17,41]. The electrocardiogram shows marked RSA with heartbeats clustering during inspiration and scattering during expiration. As the result, arterial pressure, particularly diastolic pressure, oscillates with increasing during each inspiration, suggesting oscillation in cardiac output.

If we assume that pulmonary blood flow also oscillates in synchrony with heartbeats, RSA causes such relationships between alveolar volume and capillary perfusion as shown in the left panel of Fig. 3 in each respiratory cycle. This synchronization would match alveolar ventilation and capillary perfusion throughout respiratory cycle and thus, improve respiratory gas exchange efficiency. Conversely, elimination of this relationship or further inversion of the relationship, i.e., clustering heartbeats during expiration (as shown in the right panel of Fig. 3), would deteriorate gas exchange efficiency by increasing the fraction of alveolar gas volume unable to interface with sufficient blood flow during inspiration (alveolar dead space) and the fraction of capillary blood volume unable to interface with sufficient fresh gas during expiration (intrapulmonary shunt) [18,42]. In humans, about 10% of the total blood volume is located in the lung and the pulmonary capillary blood volume participating in gas exchange at a time is only 10% of that amount [12], which is comparable to stroke volume of the...
Fig. 3. Schema showing the effects of RSA and its inversion (inverse RSA) on the relationship between alveolar gas volume and capillary blood flow during inspiration and expiration. Horizontal bows and vertical arrows indicate the volume of blood flow and the direction of gas flow, respectively. RSA improves respiratory gas exchange efficiency through matching between alveolar ventilation and capillary perfusion throughout the respiratory cycle, while inverse RSA results in increased alveolar dead space (wasted ventilation) and increased intrapulmonary shunt.

Heart. This indicates that most of the pulmonary capillary blood volume interfacing with the alveolar gas would be replaced at every heartbeat. Thus, the temporary distribution of heartbeats within the respiratory cycle could critically affect the respiratory gas exchange efficiency.

We examined if RSA actually has such effects in a previous study [21]. We developed models simulating RSA, no-RSA and inverse-RSA conditions using respiration-linked electric vagal stimulation in anesthetized dogs whose respiration was maintained by diaphragm pacing to preserve the physiological respiratory pump effects on venous return. After blocking sympathetic effect, the left vagal nerve and cephalic side of the right cervical nerve, the right cervical vagus was stimulated during each expiration for the RSA, during each inspiration for the inverse-RSA, and continuously for the no-RSA (control) conditions while calibrating the stimulation frequencies so that they made an equivalent mean heart rate per minute among the three conditions (Fig. 4). As demonstrated in the figure, arterial blood pressure showed greater respiratory oscillation under the presence of RSA compared with the no-RSA conditions, suggesting that RSA is unlikely the mechanism for stabilizing blood pressure against respiratory fluctuation of the intra-thoracic pressure. On the other hand, we observed that presence of RSA reduced alveolar dead space by 10% and intrapulmonary shunt by 51% compared with the no RSA, while the inverse RSA increased them by 14 and 64%, respectively (Fig. 5). Additionally, O₂ uptake increased by 4% with the RSA and decreased by 14% with the inverse RSA compared with the no RSA. Because tidal volume, respiratory rate, heart rate and blood pressure were the same among the conditions, this observation suggests that the presence of RSA could improve pulmonary O₂ uptake without using extra energy for circulation and respiration. These observations indicate beneficial effects of RSA on respiratory gas exchange efficiency.

Fig. 4. Polygraphs showing the ECG, femoral arterial blood pressure (ABP), vagal electric stimulation pulse train (V-STIM), and tidal volume (TV) during artificial RSA, inverse RSA and control (no RSA) in an anesthetized dog. Artificial negative pressure ventilation was performed by diaphragm pacing with electrical phrenic nerve stimulation. Artificial RSA and inverse RSA were generated by electrical stimulation of the right cervical vagus in time with expiration and inspiration, respectively. During control, the nerve was stimulated continuously at a constant rate. The frequency of the vagal stimulation pulse train was calibrated so that the number of heartbeats per minute was similar among the conditions of artificial RSA, inverse RSA and control. Reproduced from Ref. [21].
4. RSA as an intrinsic resting function of cardiopulmonary system

Improvement of respiratory gas exchange efficiency means maximum gas exchange for minimum work of the cardiopulmonary system. From this point of view, a large body of evidence accumulated about RSA supports the hypothesis that RSA is an intrinsic resting function of the cardiopulmonary system.

First, the magnitude of RSA increases with rest and decreases with strain or tension. RSA is increased in the supine position and decreased in the upright position [32,33]. It becomes greatest during sleep in a day (Fig. 6) and is greater during slow wave sleep than REM sleep [5]. It also increases with relaxation and decreases with physical and mental stresses [3,35,48].

Second, the merit of RSA on respiratory gas exchange efficiency is thought to maximize in animals and humans at rest. During rest, the cardiovascular and respiratory functions tend to shift toward directions favoring energy saving. As the oxygen demand is decreasing at rest, both heart rate and respiratory rate decrease. In such situations, RSA could further save both cardiac and respiratory energy through effectively reducing unnecessary heartbeats and wasted ventilation without compromising respiratory gas exchange performance. RSA seems a function ‘actively’ saving both cardiac and respiratory energy. On the other hand, RSA may lose its merit when oxygen demand increases with strain or exercise and indeed, RSA is strongly suppressed in such situations [3,35,48]. To increase oxygen uptake and transport, both ventilation and cardiac output need to increase. When the relative expiration period shortens with increasing respiratory rate, the alveolar gas is less likely saturated. Thus, cardiorespiratory synchronization within each respiratory cycle would lose its merit. Also, because diastolic cardiac filling is a major limiting factor of maximum cardiac output as heart rate is increasing, fluctuations in heart period such as those with RSA would be disadvantageous for increasing cardiac output.

Finally, another evidence for RSA as an intrinsic cardiopulmonary resting function is that RSA decreases with advancing age and severity of cardiac diseases. The age-dependent decline in RSA has been reported by many studies in healthy men and women at rest [23,30,43] and an increase in RSA during sleep is also reduced with aging [8]. This seems to be explained as reflecting an age-dependent reduction of functional reserve that allows the cardiopulmonary system to rest. Also, in patients with severe left ventricular dysfunction, RSA is almost disappeared even at rest and during sleep [38,50]. Furthermore, in a previous study in patients with coronary artery disease, we demonstrated that RSA at rest decreases progressively with advancing severity of coronary artery disease (Fig. 7) [20]. These observations may indicate that the cardiopulmonary system loses margin for rest with the reduction or loss of its functional reserve.

5. Association between RSA and cardiac vagal activity

As mentioned earlier, our hypothesis provides an explanation for the apparent association between the magnitude of RSA and cardiac vagal activity. More importantly, however, the hypothesis also implies that they could dissociate from each other in certain circumstances, which
is also the case. The following sections present the evidence for such dissociations and that suggestive for separate regulations of RSA from those of cardiac vagal activity.

5.1. Cardiac vagal activity and its respiratory modulation

The magnitude of RSA depends on the degree of respiratory modulation of vagal outflow to the heart. Thus, to consider the magnitude of RSA as reflecting cardiac vagal activity, we need to assume the linkage between the degree of respiratory modulation and the mean level of the cardiac vagal outflow (cardiac vagal tone).

However, evidence against this assumption is accumulating, which indicates the possible dissociation between the respiratory cardiac vagal modulation and cardiac vagal tone under certain conditions [15,16,36,53]. Goldberger et al. [15,16] demonstrated that bradycardia caused by strong baroreceptor stimulation is accompanied by paradoxical reduction in RSA magnitude. $\alpha$-Adrenergic stimulation with phenylephrine increases blood pressure and causes a bradycardia through the arterial baroreceptor reflex mechanism. The bradycardia with this reflex is mediated primarily by an increase in cardiac vagal tone; however, RSA magnitude decreases as the $\alpha$-adrenergic stimulation becomes strong. This phenomenon indicates that stimuli that increase cardiac vagal tone do not always increase RSA magnitude. Also, in recent studies of both humans and animals, we demonstrated that hypercapnia increases RSA magnitude even when it causes no detectable changes in heart rate or blood pressure [36,53]. This increase in RSA magnitude is thought to result from the direct stimulation of central chemoreceptors by increased $\text{PaCO}_2$. Furthermore, the increase in RSA magnitude was observed even when eliminating concomitant changes in respiratory rate and tidal volume [36]. These indicate that certain stimuli that do not affect cardiac vagal tone could modify RSA magnitude.

5.2. Separate regulations of RSA and cardiac vagal tone

These observations suggest that the degree of respiratory modulation of cardiac vagal outflow and cardiac vagal tone may be regulated separately and independently of each other (Fig. 8). Interestingly, studies in cats and rats reported the presence of two separate populations of cardiac vagal motoneurons that have either tonic or phasic firing pattern and topographically separated into groups in the dorsal motor nucleus of the vagus or the nucleus ambiguus [27]. C-fiber cardiac preganglionic neurons in the dorsal motor nucleus of the vagus shows regular ongoing activity that is unaffected by respiratory rhythm, while those located in the nucleus ambiguus fire with respiratory rhythm. Furthermore, the separation of these neurons occurs during embryological development as neurons that form the nucleus ambiguus migrate ventrolaterally from a more dorsomedial position, possibly equivalent of the dorsal motor nucleus of the vagus [52]. Interestingly, in axolotl, the ventrolateral relocation of the subpopulation of vagal preganglionic neurons is coincident with the onset of air breathing at metamorphosis [24].
pressure and chemoreflex ventilatory stimulation by inhalation of CO₂. The relationship between RSA and cardiac vagal function seems merely the consequence and reflection of the underlying physiological role of RSA, i.e., an intrinsic resting function of the cardiopulmonary system.

6. Conclusions

We proposed a new hypothesis that RSA is an intrinsic resting function of the cardiopulmonary system. It is getting clear that RSA is an active physiological function that bears own biological roles. RSA improves respiratory gas exchange efficiency through matching alveolar ventilation and capillary perfusion throughout respiration cycle. This function of RSA seems useful for saving cardiac and respiratory energy in resting animals and humans. Although RSA magnitude measured as the HF component of HRV is widely used as an index of cardiac vagal function, evidence indicates that RSA magnitude and cardiac vagal tone seem regulated separately and independently. The apparent association between them seems the indirect consequence of that they could appear to change parallel to each other, whenever they change in response to the resting level of the cardiopulmonary system. Our hypothesis seems more consistent with both physiological and clinical evidence about RSA and the HF component of HRV than that presuming RSA is an index of cardiac vagal activity.

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