Neural origin of the respiratory-heart rate response

JAMES D. MCCRADY, CARLOS VALLBONA, AND HEBBEL E. HOFF
Department of Physiology, College of Veterinary Medicine, Texas A & M University, College Station; and Departments of Rehabilitation, Pediatrics, and Physiology, Baylor University, Houston, Texas

The neural pathways involved in the respiratory-heart rate response (variation in the heart rate occurring simultaneously with respiration) were studied in 26 dogs, 16 cats, and 10 chickens. This study indicated that: 1) the vagi provided afferent pathways for impulses arising from receptors in the lungs or thorax to reach the cardiac regulatory centers; 2) central radiation of impulses from the respiratory centers to the cardiac regulatory centers occurred; and 3) sympathetic outflow to the heart synchronous with respiration was present.

Variations in the heart rate that occur simultaneously with respiration were first noted during the mid nineteenth century (16). Generally, cardiac acceleration accompanies inspiration, and deceleration occurs in expiration. The term "sinus arrhythmia," often applied to this phenomenon, is somewhat confusing because it does not denote a relationship between the cardiovascular and respiratory systems, and it may be used also to define cardiac arrhythmias other than those associated with respiration. The more applicable term "respiratory-heart rate response" (RHR) will be used in this paper to note this event.

Analysis of the exact relationship of the factors causing heart rate oscillations coincident with respiration is difficult and has not been fully completed. It has been suggested that one or more of the following may account for the response. 1) A wave of neural excitation spreads from the inspiratory to the cardiac-accelerator or cardiac-inhibitory center, stimulating the first, depressing the second, or both (14, 23). 2) The transient change in blood pressure that occurs with respiration affects the heart rate reflexly, via pressure receptors located in the carotid sinuses and aortic arch (15, 20). 3) The increase in inflowing venous blood during inspiration accelerates the heart through the Bainbridge reflex (3, 4). 4) The lungs are a source of impulses which exert a suppressing influence upon the cardioinhibitory center, especially during inspiration (1, 8, 19).

This paper reports the results of an investigation of the interrelationships between the peripheral and central nervous systems as they are involved in the RHR. A search was made for the afferent, efferent, and central mechanisms responsible for the response.

MATERIALS AND METHODS

Twenty-six mongrel dogs of various sizes and ages, 16 cats, and 10 chickens were used in this study. In some instances recordings were made before anesthesia, but most of the observations and recordings were made in the anesthetized animal. A tracheal cannula was inserted to facilitate administration of volatile anesthetic and artificial respiration when necessary. A carotid artery was cannulated for direct recording of the arterial blood pressure in some of the dogs.

The following physiological variables were recorded: respiration, electrocardiogram, instantaneous heart rate, and intraarterial blood pressure. An impedance pneumograph was used for transduction of respiration. The impedance changes were recorded via transthoracic electrodes, which, when properly placed, could also be used for electrocardiographic input and for triggering a cardiotachometer. A Statham model P23 series pressure transducer (Statham Transducer, Inc., Hato Rey, P.R.) was used to record blood pressure from a cannula in the carotid artery. A three-channel rectilinear Physiograph (E & M Instrument Company, Inc., Houston, Texas) was used for recording three of the physiological variables.

sinus arrhythmia; central radiation; vagal influence on heart rate and respiration; sympathetic outflow

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A magnetic amplifier model MA 61001-CY (Magnetic Amplifiers, Inc., New York, N.Y.) was employed as a stimulator. The controlling signal for the magnetic amplifier was derived from the output of the channel which recorded impedance respiration. Thus, the output of the amplifier varied according to the input signal (i.e., as the depth of respiration increased the strength of stimulus increased). The waveform of the stimulus was a half-sine wave with a frequency of 60 cycles/sec.

The following are descriptions of specific methodological aspects of the method.

Study of vagal afferents. Eight anesthetized dogs were selected for the first study. This consisted of transection of one vagus nerve in the cervical region and stimulation of the central end. Initially a Grass model SD3 stimulator (Grass Instrument Co., Quincy, Mass.) was used. Either the right or left vagus nerve was stimulated with many different combinations of frequency and strength of stimulus. The lack of change in RHR following these trials prompted the use of a magnetic amplifier as a stimulator. It was converted, as previously described, to synchronize the stimulus with respirations and to regulate the strength of stimulus according to the depth of respiration. The stimulus began with the onset of inspiration and reached its maximum at the peak of inspiration, then rapidly dissipated during expiration, reaching zero at the end of expiration. The strength of the stimulus was calibrated by passing the signal into an oscilloscope. The frequency of stimulus was constant at 60 cycles/sec.

Study of the effect of lung inflation. The effect of different levels of pulmonary inflation was studied in five dogs. The RHR was noted in these animals when they were at plane 2 of anesthesia. Artificial respiration was administered to each of these animals with a Physiograph respirator of the positive-pressure type. The respirator has a manometer that registers airway pressures. The respirator allowed for adjustments in intratrachal positive pressure and the RHR was noted at different levels of pressure from 5 to 15 cm H2O. The frequency of the respirator rate did not change at different degrees of inflation.

Study of the central influences. A group of experiments was performed in 4 dogs, 16 cats, and 10 chickens to determine the effect of decerebration on the RHR. In the dog and cat the transection of the brain stem was made immediately below the superior colliculus, using the tentorium as a guide. The chicken provided an interesting model for this study. First, the calvarium of the chicken is extremely thin, so that it could be readily opened and a large portion of the brain exposed. Second, the long cervical column is so arranged structurally that an ordinary water-hose clamp could be placed about it and tightened to prevent hemorrhage. With such a preparation, serial sections from anterior to posterior of the brain stem were easily made and the physiological responses noted.

A series of experiments designed to test the existence of a central radiation of impulses from the respiratory to the cardioaccelerator center was carried out in four dogs. The degree of RHR activity was determined in these dogs after a subcutaneous injection of morphine (10 mg/kg). They received pentobarbital sodium (30 mg/kg), their vagi were isolated in the region of the larynx, and a 1 cm section was removed from each nerve. The incision was closed and the animals allowed to recover.

Study of efferent pathways. The possible changes in RHR following cardiac sympathetic denervation were studied in five dogs. A 2 % procaine solution was injected into the stellate ganglia and the paravertebral ganglia through T-5. It is believed that this deprived the cardiac pacemaker of sympathetic impulses, since the sympathetic fibers innervating the heart appear to arise from the stellate ganglion and the paravertebral ganglia through T-5.

RESULTS

The unanesthetized animal usually had a clear RHR with the characteristics previously described by the authors. Environmental noise and the animal's movement caused marked acceleration of the heart rate, and under these conditions the RHR was not clearly detectable. The level of general anesthesia influenced the RHR in these animals, as we have previously reported.

Effect of vagal stimulation. Eight anesthetized dogs were selected for this study because they exhibited no RHR with the vagi intact. Central stimulation of either the right or left transected vagus with a Grass model stimulator failed to produce any change in the heart rate coincident with respiration. On the contrary, when a magnetic amplifier was employed as a stimulator and central stimulation of either vagus was coupled with the depth of respiration, a typical RHR was produced (Fig. 1). The strength of stimulus at which the response occurred was critical. The mean strength of stimulus found...
to produce the RHR was 10 v, with a range of 8-14 v. It must be remembered that the frequency could not be varied; thus the strength of stimulus required to initiate the effect may vary with different frequencies of stimulation because of temporal summation.

Two dogs with both vagi transected at the level of the larynx were used in an additional study. These dogs were selected because their heart rate, although fixed after transection, was relatively slow, 105 and 125 beats/min. A heart rate response synchronized with respiration was seen after stimulation. Figure 2 illustrates the typical response that occurred when either the right or left vagus nerve was synchronously stimulated. The apneustic-type breathing seen is characteristic of vagotomized dogs (12).

**Results of lung inflation.** In the animals in which the RHR was noted during positive-pressure breathing it was found that the depth of inflation influenced the response. Figure 3 illustrates that the maximum RHR occurred when the intrapulmonary inflation pressure was 6 cm H$_2$O, and it slowly regressed until at 13 cm H$_2$O pressure the response was not present, in spite of slowing of the heart rate.

**Effect of brain stem transection and of bilateral vagotomy.** The RHR persisted in the animals after transection of the brain stem. The farthest point along the brain stem that sections could be made without loss of the RHR was in the region of the pons just anterior to the medulla (5) (Fig. 4).

The rise time of the RHR was measured in seconds from the onset of the acceleration in the cardiotachogram to the peak heart rate during each ventilatory movement, and the difference between the lowest and peak heart rates was referred to as "the amplitude of the RHR response" (22). The heart rate in the morphine-treated animals prior to bilateral vagotomy was found to average 50 beats/min and the rise time and amplitude of the RHR were 1.75 sec and 25 beats/min, respectively. Three days postoperatively the same parameters were recorded in these animals following pretreatment with morphine.
FIG. 4. Photomicrograph of a tissue section taken at the point of decerebration in the chicken. Hematoxylin and eosin stain; X3.

DISCUSSION

The results of this study confirm that the RHR is dependent on a series of neurogenic influences that occur during each respiration. Many investigators had noted in acute experiments that the transection of one vagus nerve did not abolish the RHR, whereas transection of both did (1, 10, 11). These observations were confirmed in this study. Vagal stimulation, of course, may vary during normal respiration with the degree of inflation; this was illustrated in the experiments carried out to test the effect of different degrees of expansion of the lungs. It is interesting that with increase in inflation, the RHR became less manifest.

The studies prove the participation of the vagus nerve in the RHR, but since the response is detectable after chronic bilateral vagotomy it is necessary to discuss the extent of other influences on the RHR.

The results of transection of the brain stem show clearly the importance of this center. That the RHR was noted in the chicken after transection of the brain stem was of interest, since the respiratory system contains a series of air sacs which communicate with the lungs, and inspiration is a passive act (18).

Other factors indicative of the importance of the central nervous system in the RHR response were noted. Figure 5 shows an instance in which changes in the heart rate similar to those associated with the RHR are present during a period of apnea. Figure 5 clearly exhibits an interesting relationship between the blood pressure and
the heart rate in which there is a simultaneous increase of both. It should also be noted that both inspiration and expiration were apparently related to acceleration of the heart. Similar oscillations were seen in the blood pressure during periods of apnea in other studies.

A most significant aspect of this study is the persistence of the RHR in the vagotomized preparation (Fig. 6). Anrep et al. (2) commented that the simplest way to demonstrate the existence of a central respiratory arrhythmia with participation of the acceleratory fibers of the sympathetic would be to determine whether the arrhythmia persists after section of the cervical vagi. They stated, “Vagotomy leads, however, to such an acceleration of the heart that it is difficult to notice a difference between the inspiratory and expiratory heart rate. In fact, after having carefully measured a great number of records, we believe that the heart beats, under these conditions, at a uniform rate.” It is probable that the sympathetic tone had decreased in the chronic vagotomized preparations of the studies reported here, for the heart rate averaged 166/min immediately after vagotomy and 144/min 3 days later. The decrease in the amplitude of the RHR of the vagotomized animal can in part be attributed to the increase in heart rate. However, the slowing in the average rise time from 1.75 to 3 sec would indicate that the vagi play an important role in initiating the response. Figure 7 illustrates a similar condition, where the afferent inflow is apparently responsible for the initiation of a phenomenon but it is not at all times essential for it to occur. Shown is the relationship between the shivering process, recorded via an electromyograph from the hindlimbs, and respiration. Shivering began with the onset of inspiration and stopped at the end of expiration. This phenomenon may be thought of as another example of central radiation associated with respiration.

Those investigators who have advocated the existence of a central origin of the RHR have postulated that the impulses radiating from the respiratory center produced the response by stimulating the cardioinhibitory center. This would indicate that the central arrhythmia was dependent solely on the diminution of vagal tone during periods of inspiration. The studies in which the vagi were sectioned disproved this and added evidence in support of those investigators who recorded action currents in the sympathetic fibers that were synchronous with respiration (6, 7, 21). The results of sympathetic denervation clearly showed the presence of sympathetic outflow to the heart synchronized with respiration and are in agreement with recent observations of increased myocardial excitability during inspiration in the atropinized animal receiving an infusion of calcium chloride (Dietzman et al., to be published).

These studies suggest that: 1) the vagi provide important afferent pathways for impulses arising from receptors in the lungs or thorax to reach the cardiac regulatory centers; 2) central radiation of impulses from the respiratory centers to the cardiac regulatory centers occurs; and 3) there is sympathetic outflow to the heart synchronized with respiration. Changes in the rise time and amplitude of the RHR occurring with these various experimental procedures indicate that the conventional RHR response is dependent on these three conditions existing concurrently in the presence of a tonic background of bradycardia of vagal origin, and that during inspiration this vagal activity is centrally suppressed while the sympathetic is stimulated.

It is not likely that in the central nervous system one action should take place without the simultaneous central
suppression of the antagonistic action. Therefore, both vagal suppression and sympathetic stimulation may ac-

REFERENCES
