Basic Oscillating Mechanism of Cheyne-Stokes Breathing

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ABSTRACT

Cheyne-Stokes breathing has been induced in 30 dogs by inserting a circulatory delay system between the heart and the brain to prolong the transit time of blood from the lungs to the brain. The duration of each cycle of Cheyne-Stokes breathing increased proportionately with the volume of the delay system and decreased as the perfusion pressure to the brain was increased. Periodic variations in oxygen and carbon dioxide concentrations in the blood were found to be in appropriate phase to stimulate the respiratory centers at the time of maximal ventilation. This supports the theory that Cheyne-Stokes breathing is due to oscillation of the respiratory control system.

The physical characteristics of Cheyne-Stokes breathing suggest that it might be due to oscillation of the basic regulatory mechanism of respiration. One theory of its cause is the following: the patient overventilates for a few seconds, and this changes the blood gas concentrations until the respiratory center loses its stimulation; as a result, he underventilates, and the blood gases change again; consequently, he overventilates once more, and the cycle continues (1-6). The present study has been designed to help answer whether or not this theoretical oscillating mechanism is the actual basis of Cheyne-Stokes breathing.

The results to be reported are based on periodic respiration established in dogs by inserting a circulatory delay system between the lungs and brain. Also, additional studies have been carried out to establish phase relationships between blood gas concentrations and the cycles of periodic breathing.

METHODS

Thirty dogs anesthetized with sodium pentobarbital, heparinized with 5 mg/kg of heparin, and cannulated appropriately for recording blood pressures and respiration on a kymograph were used. To establish Cheyne-Stokes breathing, the flow of blood from the lungs to the brain was delayed by passing it through long plastic tubes connected between the proximal carotid arteries and the distal carotid or vertebral arteries. The most efficient delay system was one constructed of a long plastic tube wrapped randomly about many pegs in a board to obviate any streamlining effect. Then, to prevent blood flow into the respiratory center through channels other than the delay system the soft tissues of the neck were transected with a cautery. Also, a perfusion pump was placed in the delay system to raise the pressure in the perfused arteries of the head thereby blocking any collateral blood flow up the spinal arteries.

Changes in the blood gas concentrations during induced Cheyne-Stokes breathing were measured in three dogs by a cuvette type oximeter, in two dogs by a continuously recording photoelectric hemoglobin saturation meter, and in two dogs by Van Slyke-Neill manometric analysis of serial blood samples for carbon dioxide.

RESULTS

Damped Oscillation of the Cheyne-Stokes Mechanism. In all preparations in which a delay system was used, damped oscillations such as those shown in figure 1 were obtained. These could be induced by hyperventilating the dog for 1–2 minutes, by obstructing his respiratory passages for a minute or more, by suddenly increasing or decreasing the blood pressure to the brain, or by any other circumstance which would cause hyperventilation or apnea for a short interval of time. Sometimes these damped oscillations lasted no longer than one or two cycles, whereas at other times, they lasted six, eight or more cycles.

Spontaneous Oscillation of the Cheyne-Stokes Mechanism. Spontaneous oscillations, such as those illustrated in figures 2 and 3,
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Figure 1. Damped Cheyne-Stokes breathing in a dog with a delay circuit between the heart and the brain. Damped oscillation was induced by a 1-min. period of hyperventilation immediately prior to the beginning of the record.

Figure 2. Spontaneous and continuous periodic breathing in a dog with a delay circuit between the heart and the brain. (Time intervals, 1 min.)

occurred in 10 of the preparations. The preparations which oscillated spontaneously were those with very active respiratory centers and with long delay intervals between passage of blood through the lungs and through the brain. The duration of each cycle of oscillation varied from 2 to 10 minutes, the exact value depending on the delay time between the lungs and brain (40 sec. to 5 min.).

Relationship of the Delay System Volume to the Duration of Each Cheyne-Stokes Cycle. The delay system volume was varied in different animals from 140 to 650 ml. In general, the greater the volume the longer the cycles, but this correlation was not exact because of different rates of cerebral blood flow in different animals. In four dogs which were exhibiting spontaneous oscillations, the volume of the delay system was changed while these oscillations were taking place. Figure 3 illustrates the proportional effect on the duration of the cycles when the volume in one experiment was suddenly changed from 650 ml to 360 ml. Precisely this same proportional effect occurred in the other experiments.

Relationship of Cerebral Arterial Pressure to the Duration of Each Cheyne-Stokes Cycle. The rate of blood flow through the delay system was increased and decreased by changing the perfusion pressure in the head. Table I shows the relationship of the periods of oscillation to the perfusion pressures. In each animal it is evident that decreasing the perfusion pressure increased the duration of the cycle. This correspondence was almost a proportional inverse relationship between perfusion pressure and duration of the cycle.

Phasic Relationships of Blood Gas Cycles and Respiratory Cycles. Oxygen or carbon dioxide concentrations were measured in seven experiments during the periodic respiration. Figure 4A illustrates a typical relationship in one dog between the respiratory cycle and the blood oxygen saturation in the distal portion of the delay circuit, and figure 4B illustrates the same relationship in the proximal portion of the delay circuit. An increase in the ventilatory rate caused the blood oxygen to increase immediately in the proximal portion and to increase in the distal portion almost exactly one-half an oscillatory cycle later. The degree of respiratory activity lagged an average of 20° behind the changes in oxygen saturation in the distal end of the delay circuit, which illustrates that the blood gases were always in appropriate phase for stimulation of the respiratory center during the hyperpneic phase of the Cheyne-Stokes breathing.

Identical phasic effects were observed for the relationship of blood carbon dioxide to the

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<th>Dog No.</th>
<th>Cerebral Arterial Pressure, mm Hg</th>
<th>Duration of Cycle, sec.</th>
<th>Dog No.</th>
<th>Cerebral Arterial Pressure, mm Hg</th>
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Fig. 3. Effect of delay system volume on duration of each cycle of oscillation. (Time intervals, 1 min.)

Fig. 4. Phase relationship of blood oxygen concentration to the depth of respiration: A, at distal end of delay circuit; and B, at proximal end of delay circuit.

respiratory cycles except that the carbon dioxide concentrations rose when the oxygen concentrations fell and vice versa.

DISCUSSION

The major value of the present study has been the demonstration that increased transit time for passage of blood from the heart to the respiratory center can cause periodic breathing similar to or identical with Cheyne-Stokes respiration in the human being. This is the first time that such has been achieved in animals by this method, though clinically many patients with Cheyne-Stokes breathing are known to have prolonged circulation times (6). It seems evident, then, that delay in the flow of blood from the heart to the brain is in itself sufficient cause for periodic breathing.

In view of the theory of oscillation of control mechanisms (7, 8), the cause of the periodic breathing in these experiments is probably oscillation of the respiratory control system induced as a result of decreased damping. This may be explained as follows: when one suddenly begins to hyperventilate the alveolar \( \text{pO}_2 \) begins to rise, and the \( \text{pCO}_2 \) begins to fall. The concentrations of these gases also begin to change in the blood and other body fluids, but these changes lag slightly behind those in the lungs. This slowness of the gas concentrations in the alveoli and fluids to ‘follow’ the increases and decreases in pulmonary ventilation ‘damps’ the respiratory control system. Normally, before the gas concentrations in the blood have time to change to an extreme extent the first portions of blood affected by the change in ventilation will have already reached the respiratory center, and, as a result, the rate of pulmonary ventilation will have returned toward a normal mean value. Because the transit time for blood flow from the lungs to the brain is normally only a few seconds, extreme changes in blood gas concentrations almost never occur before the rate of pulmonary ventilation readjusts to or almost to a normal mean value. Therefore, the tendency for blood gas changes to drive the control system beyond the mean rate of ventilation is usually very slight.

On the other hand, when the circulation time from the lungs to the brain is greatly increased,
the respiratory center reacts only after a prolonged period of delay to changes in pulmonary ventilation, which allows the alveolar and blood gases to continue changing for increased intervals of time. As a result, the changes in blood gas concentrations become far more intense than normally. Then the blood with drastically changed gas concentrations reaches the respiratory center and causes a drastic 'overshoot' in the respiratory control mechanism. The ventilatory rate changes in the opposite direction, and opposite changes then begin to occur in the concentrations of alveolar and blood gases. Here again, the prolonged delay time in blood flow prevents activity of the respiratory center from increasing the effectiveness of at least one of the normal damping factors of the respiratory control system.

The phasic changes in blood gases as determined by a cuvette oximeter, by a hemoglobin saturation recorder, and by Van Slyke-Neill manometric analysis all support the concept that the periodic breathing of these experiments was due to alternating changes in the blood gas concentrations. These changes occurred in the proximal portion of the delay system immediately after the changes in the rate of pulmonary ventilation. On the other hand, the measurements of phasic changes in the distal portion of the delay system showed that the respiratory center responded to changes in blood gases immediately after the blood left the delay system to enter the arteries of the brain.

Another postulated explanation for Cheyne-Stokes breathing besides the oscillatory theory presented above is that it is due to periodic waxing and waning of respiratory excitability initiated entirely within the neuronal circuits of the hindbrain (9). The present demonstration that a delay circuit between the lungs and the respiratory center will cause periodic breathing of the Cheyne-Stokes type is opposed to this theory. Also, the fact that changes in the delay time will cause a change in the periodicity is against this theory because oscillation originating entirely in the brain should not be dependent upon phasic changes in the circulating blood. Finally, the demonstration that activity of the respiratory center increases and decreases in response to changes in gas concentrations in the blood leaving the distal portion of the delay circuit is in accord with the theory that the respiratory control system is oscillating but not with the theory that an intrinsic hindbrain periodicity exists.

If decreased damping of the respiratory control system is an adequate cause of Cheyne-Stokes breathing, then any condition which might decrease respiratory damping could cause this type of breathing. This fact possibly explains many of the known clinical causes of Cheyne-Stokes breathing such as (6, 9–12):

1. increased circulation time, which increases the delay time from the lungs to the brain,
2. increased volume of blood in the left heart, which also increases the delay time,
3. decreased vital capacity, which decreases the storage of alveolar gases and thereby decreases the 'lag time' in the changes of alveolar and blood gases following changes in pulmonary ventilatory rate, and
4. any factor which might damage neuronal circuits concerned with damping the respiratory control system—such circuits are only theoretical at present, but this is one possible explanation of the periodic breathing that results in many instances of brain damage.

REFERENCES