

THE MECHANISM OF CHEYNE-STOKES RESPIRATION *

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The unusual breathing pattern characterized by cycles of hyperventilation and apnea was first described by Cheyne in 1818 (1) but wider attention was attracted to the phenomenon by Stokes in his work "The Diseases of the Heart and Aorta" in 1854 (2). This pattern is most commonly seen in patients with heart disease. The form of cardiac dysfunction associated with this respiratory disorder is characterized by left ventricular dilatation, pulmonary congestion, and a low cardiac output. Hypertensive disease or ischemic heart disease are the usual etiological factors.

The underlying mechanism of this disorder has been the subject of debate since Cheyne described it in a man with "heart disease and apoplexy." Stokes implicated heart disease more specifically by stating, "But there is a symptom which appears to belong to a weakened state of the heart, and which, therefore, may be looked for in many cases of fatty degeneration. I have never seen it except in examples of that disease. The symptom in question (cyclic respiration) was observed by Dr. Cheyne although he did not connect it with the special lesion of the heart."

There is still no general agreement concerning the cause of this type of cyclic respiration; some consider the altered breathing pattern primarily neurogenic, others inveigh a circulatory disorder. Any proposed mechanism must be able to account for the consistent findings seen in this disorder: *a*) the long duration, often years, of the respiratory dysrhythmia, frequently without obvious evidence of central nervous system disease; *b*) the absence of cyanosis or polycythemia in spite of periods of prolonged apnea; *c*) mental clarity, or absence of altered sensorium during the apneic phase (described by Stokes as "the long continued cessation of respiration yet without any suffering

on the part of the patient"); *d*) the crescendo-decrescendo respiratory pattern; *e*) return to normal breathing when circulation is improved.

Pryor (3) demonstrated a phasic temporal shift between ventilatory function and arterial blood gas values in individuals with Cheyne-Stokes (C-S) respiration and heart disease with arterial oxygen saturation highest during the period of apnea. This was not true in patients with intracranial hemorrhage or increased intracranial pressure who also exhibited intermittent respiration. He assumed that in C-S breathing an increased lung-to-brain circulation time caused oscillatory variations in arterial saturation resulting from a delayed feedback of the ventilatory effects (output) to the respiratory center (input) (Figure 1). This mechanism implies that in a given instance well ventilated blood does not mix well with the poorly ventilated blood and causes the respiratory center(s) to be exposed for relatively long periods to blood which is alternately well or poorly ventilated. This concept had been suggested earlier by Klein in 1930 (4), but in 1932 Anthony, Cohn and Steele (5) publishing findings similar to those predicted by Klein, did not reach this same conclusion. No further observations were available until Guyton, Crowell and Moore (6) demonstrated that when the lung-to-brain circulation time was artificially increased in an otherwise normal dog, oscillatory, or C-S respiration could be induced.

More recently, Brown and Plum (7) observed hypocapnea in patients with cyclic respiration of the C-S type and suggested that this type of breathing is primarily neurogenic in origin. Review of the data of Pryor also shows the relative hypocapnea described by Brown and Plum. The divergent conclusions derived from seemingly consistent observation suggested that both simultaneous and continuous measurements of respiratory and blood gases together with estimates of circulation times from lung to artery would be desirable to resolve the differences in interpretation. In

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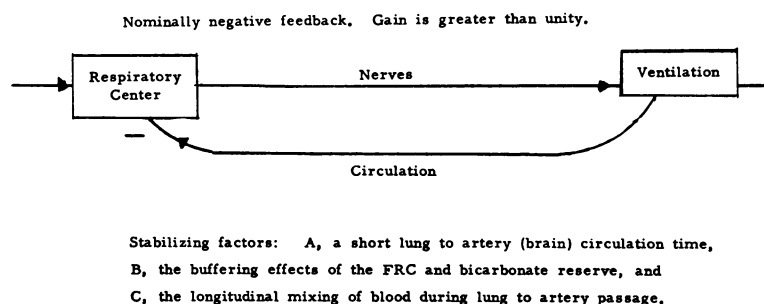


FIG. 1. A SCHEMA OF THE RESPIRATORY CONTROL SYSTEM. The time delay introduced by the feedback pathway via the circulation is considered to be much greater than the temporal delay at any other portion of the loop.

addition to a re-examination of the nature of cyclic respiration it appeared desirable to study the specific effect of large cyclic variations in blood gases and pH on respiratory center function.

METHODS

Nine patients with typical Cheyne-Stokes respiration were studied over a 2-year period. Although all gave evidence of heart disease with some degree of failure (Table I) none complained of orthopnea at the time of study. All measurements were made with the patient supine. After infiltration with 1 per cent procaine, percutaneous femoral arterial puncture was performed and arterial blood was sampled continuously (0.5 ml per second) through a Wood cuvet oximeter which in turn led to a galvanometer system and allowed continuous graphic recording of variations in arterial oxygen saturation¹ with an approximate 1-second delay due to sampling dead space. Multiple arterial samples were also ob-

tained for analysis by the method of Van Slyke and Neill for CaO_2 and CaCO_2 .

pH was determined by a Cambridge model R pH meter, and PaCO_2 calculated from Singer and Hasting's nomogram. Ventilatory activity was recorded in Patients 1-3 by means of a thermocouple near the external nares. In Patients 4-9 expired CO_2 was continuously monitored by an infrared CO_2 meter² (Figures 2 and 3). In Patient 4, measurements were made during right-heart catheterization. In this patient cardiac output was determined by the direct oxygen Fick method. Lung-to-artery mean circulation time was estimated from indocyanine dye curves by dye injection into a peripheral branch of one pulmonary artery and sampling from the femoral artery (8). In Patients 5-9 cardiac output was measured by the dye method, using venous injection. Lung-to-artery circulation time was estimated by measuring arm-to-lung circulation time (ether) and subtracting this value from the arm-to-artery circulation time obtained by the dye method or by injection of Decholin.

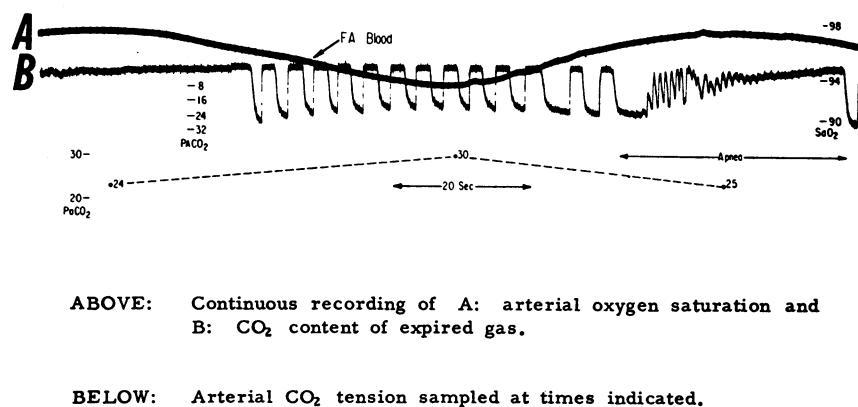


FIG. 2. SIMULTANEOUS, CONTINUOUS RECORDING OF ARTERIAL OXYGEN SATURATION (OXIMETER) AT TOP AND EXPIRED CO_2 (PaCO_2) IN THE CENTER. PaCO_2 derived from multiple arterial samples is indicated by the dashed line. Pulmonary artery to systemic artery circulation time was 48 seconds. Period of respiratory cycle was approximately 100 seconds (Patient F.F.).

¹ Waters Corp., Rochester, Minn.

² Beckman model LB-1.

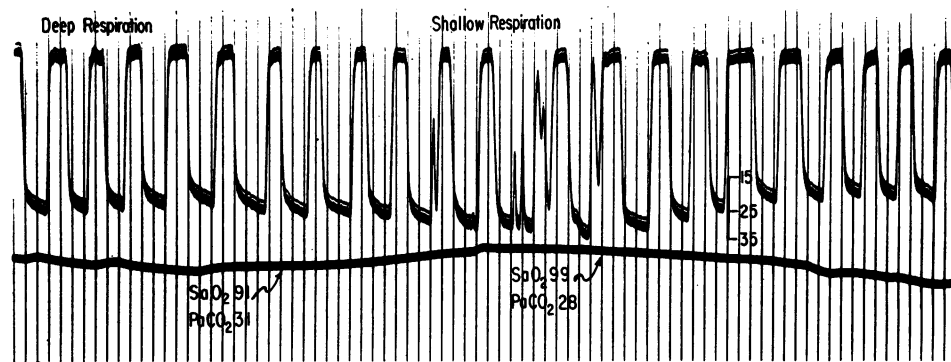


FIG. 3. AT TIME OF RECORDING COMPLETE APNEA DID NOT OCCUR. Variations in depth and rate of respiration have a period of approximately 60 seconds. The lung-to-artery circulation time was estimated to be 28 seconds. The lower line represents continuous recording of SaO_2 (oximeter). Blood gas values were obtained by (Van Slyke) chemical analysis (Patient D.D.).

Seven patients expired within 2 to 24 months after study. In five, complete postmortem examination was obtained.

RESULTS

Table I shows the clinical characteristics and postmortem data of the patients studied. All but one were males and all were older than 59 years. Heart disease with left ventricular dilatation was present in all. Postmortem examination of H.D. revealed multiple cerebral and midbrain infarctions. In W.M. friable mural thrombi were found in the left ventricle. Postmortem examination was not obtained in C.B. but a few weeks prior to the physiological study he had manifested mental confusion, and subsequent examination of cerebro-

spinal fluid showed xanthochromia and other findings consistent with a recent cerebrovascular accident. S.G. also expired several months after the study. No autopsy was performed but it was clear that she had suffered a left hemiplegia, apparently caused by a cerebral arterial thrombosis. In F.F., D.D. or C.H. there was no clinical evidence for cerebrovascular disease. D.D. and F.F. died in heart failure and at autopsy neither had any evidence of organic brain disease. G.Y. and R.S. suffered from hypertensive cardiovascular and renal disease with azotemia and renal acidosis. No organic brain disease was seen in R.S. at autopsy. G.Y. is living and shows no neurological abnormalities.

TABLE I
*Clinical, laboratory and postmortem findings in patients with Cheyne-Stokes respiration **

Patient, Age, Sex	Clin. diag.	Duration	Sensorium	Neurol. sign	X-ray		ECG	Postmortem	
					LVE	PC		Heart	Brain
1. C.B., 81 ♂	HCVD, MI	8 mos	Clear	Pastpointing, term. hemipl.	4+	2+	RBBB	Died, no P.M.	
2. H.D., 77 ♂	ASHD, azot.	12 mos	Confused	Poor memory	1+	1+	LVH	Mult. MI, LVE	Mult. small infarct.
3. W.N., 73 ♂	ASHD, azot., MI	4 mos	Clear	Diffuse polyneuritis	1+	2+	RBBB, old inf.	LVH, thromb.	No ocl., vasc. dis.
4. F.F., 70 ♂	RHD, mitral incomp., MI	2 yrs	Clear	0	4+	4+	LVH	LVE, MI	No ocl., vasc. dis.
5. G.Y., 67 ♂	HCVD, azot.	2 yrs	Clear	0	4+	4+	LVH	Alive	
6. C.H., 65 ♂	HCVD ASHD	2 yrs	Clear	0	3+	1+	LVH	Alive	
7. D.D., 59 ♂	RHD, aortic stenosis	2 yrs	Clear	0	4+	4+	LVH	Rheum. ao. stenosis	No abnorm.
8. R.S., 52 ♂	HCVD, azot.	?	Confused	0	3+	3+	LVH	LVH	No abnorm.
9. S.G., 75 ♀	RHD, mitral incomp.	3 mos	Aphasic	L. hemipl.	2+	1+	LVH	Died, no P.M.	

* LVE = left ventricular enlargement; PC = pulmonary vascular congestion; HCVD = hypertensive cardiovascular disease; MI = myocardial infarction; azot. = azotemia; ASHD = arteriosclerotic heart disease; RBBB = right bundle branch block; LVH = left ventricular hypertrophy.

TABLE II
Circulatory parameters in Cheyne-Stokes respiration

Patient	VPRC %*	C.O.	Cycle length	Circ. time vein to art.	Circ. time lung to art.
		L/min	sec	sec	sec
1. C.B.	43		88		
2. H.D.	49		70		
3. W.M.	39		60		
4. F.F.	43	2.9	98	67	47
5. G.Y.	43	2.6	50	34	27†
6. C.H.	50	3.1	50	38	24†
7. D.D.	44	2.2	60	40	28†
8. R.S.	21		39	23	18†
9. S.G.	51	2.3	80	49	

* Volume of packed red blood cells, %.

† Indirect estimation of lung-to-artery circulation time was obtained by subtracting the arm vein to lung time (ether) from the vein-to-artery time (indocyanine green dye).

Physiological data are summarized in Tables II and III and Figures 2 and 3. A complete cycle (period) lasted from 48 to 98 seconds. SaO_2 was highest during midapnea and at its lowest value during midhyperpnea. Conversely, values for PaCO_2 were lowest during apnea and highest during hyperpnea. No value of PaCO_2 was above the normal range. Arterial desaturation was found in G.Y., R.S., and S.G., but only during hyperpnea. Despite arterial oxygen desaturation in these patients, PaCO_2 was below normal.

Examination of the expired gas analysis in Patients 4-9 showed that, in contrast to the arterial

blood gas values, as the period of hyperpnea began, PaCO_2 was at a maximum and fell as the respiratory rate and tidal volume increased, only to rise again as rate and depth decreased and apnea recurred. At the time the alveolar gas contained the lowest values for CO_2 tension, the arterial blood demonstrated the highest value for PaCO_2 .

Lung-to-artery circulation time was always prolonged (Table II) and generally measured about 50 per cent of the respiratory cycle length.

Although all patients had exhibited classic cyclic respiration with definite periods of apnea, at the time of study Patients C.H. and D.D. showed only a cyclic variation of depth and rate without complete apnea. Figure 3 and Tables II and III indicate that this "forme fruste" manifestation is identical with the typical C-S respiration in the temporal relationships between respiratory and blood gases.

DISCUSSION

These results in general agree with those expected from the theoretical assumptions made by Klein (4) and the published findings of both Anthony and colleagues (5) and Pryor (3). In addition, a prolonged lung-to-artery circulation time which was equal to one-half the cycle period could be demonstrated. This suggests a cause and effect relationship between cycle period and this parameter. The phasic lag between ventilatory activity

TABLE III
*Arterial and alveolar gas values in Cheyne-Stokes respiration **

Patient	Sao_2		pH		CaCO_2		PaCO_2		PaCO_2 (during hyp.)		
	Ap.	Hyp.	Ap.	Hyp.	Ap.	Hyp.	Ap.	Hyp.	Onset	Mid	End
1. C.B.	99	93	7.60	7.43	40.0	46.0	19	30			
2. H.D.	97	91	7.47	7.44	43.0	48.5	28	31			
3. W.N.	No blood gas data except random samples which showed Sao_2 above 90%										
4. F.F.	97	94	7.56	7.50	43.0	47.0	25	30	30	25	30
5. G.Y.	96	77	7.48	7.43	37.0	42.0	24	28	30	24	30
6. C.H.	98†	94	7.45†	7.43	35.0†	39.0	23†	28	32†	20	30†
7. D.D.	99†	91	7.48†	7.46	46.6†	48.2	28†	31	30†	18	30†
8. R.S.	81	76	7.56	7.50	50.5	53.2	25	32	32	25	30
9. S.G.	92	81	7.43	7.40	34.6	41.4	23	30	30	18	30
\bar{X}	94.9	87.1	7.49	7.45	41.2	45.7	24.4	30.0	30.6	21.7	30
Grand \bar{X}	91		7.47		43.5		27.2			26.0	
Normal (S L C)	91-93		7.40				32.0			32.0	

* Ap. = apneic; Hyp. = hyperventilatory period; Sa = saturation, %; Ca = arterial content, vol. %; Pa = arterial tension, mm Hg; PA = alveolar tension, mm Hg.

† Depth of respiration varied without apnea at time of study.

and arterial blood gases is strikingly demonstrated by the simultaneous continuous recording of ventilation and of arterial oxygen saturation, and by the continuous monitoring of expired CO_2 together with multiple blood gas samples for PaCO_2 .

Certain features of this investigation were particularly interesting, and their possible importance will be further considered below: *a)* the age and sex of the group studied; *b)* the usual absence of arterial blood oxygen desaturation throughout the cycle; *c)* the low mean levels of PA_{CO_2} and PaCO_2 ; *d)* the evidence in some cases for coexistent cerebral vascular disease.

a) All patients included in this study were above 52 years of age but this may have been due to bias of sample in a County Hospital population. Other reports have included patients as young as 25 (3). All patients reported in References 1, 3, and 5 were males. This high relative incidence in males has not received previous comment.

b) The absence of significant arterial oxygen unsaturation (except in Cases 5, 8, and 9) is in agreement with other reports (3, 5, 7). None of the patients appeared cyanotic during any portion of the respiratory cycle, nor was clubbing found. These findings rule out persistent anoxemia as a primary mechanism for respiratory control in these subjects, in contrast to its presumed role in cases of cerebral contusions and brain tumor (3). There is, however, evidence that mild anoxemia potentiates the effects of PaCO_2 on the carotid body or medullary receptors (9, 10).

c) Previous studies have shown varying degrees of hypocapnea (3, 7). In the present study analysis of end-tidal gas reveals a lowered PA_{CO_2} at all times. Furthermore, PA_{CO_2} falls to even lower levels during hyperpnea. In Figure 2 end-tidal PA_{CO_2} of the first breath following apnea shows a value below the expected normal, despite more than 30 seconds of apnea. It is attractive to imagine venous blood slowly passing through the pulmonary capillary bed and contributing CO_2 to an alveolar volume ventilated so well that even after brief apnea PA_{CO_2} is less than normal. By inference, the observed effect of cyclic respiration is equivalent to chronic mild hyperventilation. This problem will be considered in detail later.

d) Patients 3-8 did not show gross or histological evidence of cerebrovascular disease. However, the presence of severe cerebrovascular dis-

ease at postmortem examination in Patient 2 and inferred from clinical signs in Cases 1 and 9 introduces a confusing element. Several interpretations are open for consideration. First, the presence of central nervous system disease might be part of a generalized ischemic vascular disease without causal relationship to C-S breathing. Second, the central nervous system disorders act in a permissive manner, allowing cyclic respiration to occur if circulatory abnormality coexists. A third concept would make the neurological defect the primary and only essential defect, the cardiovascular disorder being coincidental but not essential. The finding of abnormal circulatory function in all patients studied, and the freedom from cerebrovascular or other organic brain disease in six of the nine patients studied, would rule out the third concept and severely vitiate the second, but would be compatible with a primary circulatory disorder. The discussion to follow is directed toward a delineation of the roles of circulation and of nervous control in cyclic respiration as observed in the patients studied. The physiological parameters of respiratory control will be compared with analogies utilized in engineering control system analysis. Relationships will be developed between important physiological parameters and the more easily studied electrical analogue.

Analysis of components of the respiratory control system

1. Although many afferent stimuli influence the level of respiratory activity, respiration normally is controlled from a medullary respiratory center primarily sensitive to the tension of CO_2 . This does not exclude other controlling factors, such as changes in arterial oxygen tension or in arterial pH, whether they be additive (9) or synergistic (10, 11).

2. The time constant for the equilibration of blood gases with the chemoreceptors of the brain stem (or carotid artery) is short compared with the time constant of other components of the control system. Variations in arterial blood O_2 and CO_2 tension are considered to be rapidly approached by equivalent variations in the chemoreceptors.

3. The sensing mechanism at the receptor site directly or indirectly causes appropriate neuro-

muscular operations which in turn affect ventilatory activity. The transmission time of the efferent controlling impulse (neuromuscular) is negligible. The medullary center presumably regards a deviation in P_{CO_2} from a reference value as an error signal and acts to reduce this deviation.

An important characteristic of control systems is the ratio of output to input or the "gain" of the amplifier component. When the amplifier component of a system acts in such a manner that a disturbing influence (input) results in a response (output) which, in the absence of a feedback signal would be greater in magnitude than the input, then the ratio of output to input will exceed one, and the gain becomes some value greater than unity. In general, a high gain amplifier component in a control system acts to provide rapid response to changing conditions as well as close adherence to a reference input value (12, 13). The respiratory control system responds to an increase in P_{CO_2} by increasing ventilation and lowering the P_{CO_2} of pulmonary capillary blood. This property is necessary for control and is called "negative feedback."

4. Since the control of Pa_{CO_2} within small limits is presumably the goal of the respiratory control system, transmission of the "negative feedback signal" is required to reflect the increase or decrease of alveolar ventilation. This feedback pathway entails the transport of pulmonary capillary blood to the brain via the left ventricle. This transport time is closely related to the lung-to-artery transit time. A schematic representation of the control system is depicted in Figure 1.

5. Because of the finite time required for transmission of feedback and the greater than unity gain, the system as described would be unstable at certain frequencies and would result in oscillating fluctuations in ventilatory activity (12, 13). Several stabilizing mechanisms operate. In addition to a short lung-to-brain circulation time, longitudinal mixing of blood during transit from lung to heart to brain would decrease the effective transit time and minimize the effects of variable ventilation. There is evidence that this mixing is far from complete (14). More efficient buffers exist which tend to maintain constant blood gas levels despite transient variations in ventilation. One is the functional residual capacity (FRC). This volume acts as a damper (15) in that it permits

brief periods of hypo- or hyperventilation with minimal variation in blood gases. Another is bicarbonate reserve which likewise minimizes the alteration of Pa_{CO_2} if CO_2 excretion is temporarily greater or less than CO_2 supplied to the pulmonary capillaries. As a consequence, under normal circumstances the control system, potentially oscillatory because of gain and delayed feedback, is damped and a nearly optimal balance is struck between stability and speed of response.

One might expect that infringement of the total lung volume by cardiac enlargement, caval distention and congestion or diminution of FRC in the supine position (16) would decrease the effectiveness of this stabilizing factor. A potentially oscillating system then might oscillate only with a change from erect to supine position. This may be a factor in the observations of Altschule and Iglauer (17) which indicate that C-S respiration is enhanced by a change from sitting to supine position.

Patients, 2, 3, 5, and 8 showed mild to severe renal acidosis. The attendant alkaline reserve in these patients would allow greater variation in Pa_{CO_2} for a given transient change in rate of excretion as compared with the normal. The tendency toward mild compensated respiratory alkalosis in chronic congestive heart failure would cause a decrease in alkaline reserve when renal function is normal.

The following paragraph uses the analogy between the respiratory control system and an electrical control system with components of amplification, negative feedback, and finite delay in the feedback loop. Although we have attributed "negative feedback" to the biological control system (Figure 1), if the feedback signal is delayed so that it returns to the sensing center with a phase angle of more than 90° from ideal, "positive feedback" is produced. A similar electrical system would be considered to have positive feedback and greater than unity gain. Both systems would oscillate at a frequency related to the time required for a complete circuit (12, 13). By such an analogy C-S respiration would occur whenever the damping factors (FRC, alkaline reserve, short lung-to-brain transit time) are sufficiently compromised.

A necessary consequence of the conclusions noted above should be the occurrence of cyclic

respiration in normal individuals whenever the stabilizing conditions are compromised. Although this study deals with C-S respiration in heart disease, it should be recalled that cyclic respiration is often seen in mountaineers, particularly during sleep, either at altitudes over 20,000 feet or at lower levels if acclimatization is not complete. In 1909, Douglas and Haldane studied the cyclic respiration which prevailed transiently after apnea was induced by voluntary hyperventilation (15). Alveolar gas analysis at the onset of the hyperpneic phase indicated both hypocapnea and hypoxia. Although the FRC and bicarbonate reserve were recognized as having a "flywheel action," Douglas and Haldane did not consider the possible role of circulatory transit time, probably because information concerning the latter was not available. They proposed that "hunting" of a respiratory center (made more sensitive by hypoxia) occurs because of slow movement in and out of the interstitial fluid of the center. Under the condition of sitting quietly after forced hyperventilation, these authors show that the cycle period is between 28 and 32 seconds. In addition, cyclic respiration may be induced in normal subjects exposed to

mild or moderate hypoxia (10). Figure 4 is obtained through the courtesy of Dr. Ulrich Luft, Department of Physiology, Lovelace Foundation, Albuquerque, N. M. It is a record of ventilation in a normal volunteer breathing 10 per cent oxygen in nitrogen for 2 hours at a barometric pressure of 630 mm Hg. Note the periodic character of the respiration, whether with complete apnea (top line) or with variation in depth (along center of lower tracing). In such normal individuals the periods are short (18 to 22 seconds) and allow only a few respiratory cycles before apnea recurs. If the cycle period were a function of the lung-to-brain circulation time, as inferred in the discussion of C-S respiration in heart disease, this time should be 9 to 11 seconds. This is approximately the circulation time expected in the normal supine adult male subjected to moderate anoxia.

In like manner, the cyclic respiration reported by Douglas and Haldane would require a somewhat longer lung-to-brain circulation time; i.e., 14 to 16 seconds. This time, a few seconds greater than that theorized from Figure 4, would be expected in an older subject quietly sitting.

It is attractive to assume that Figure 4 repre-

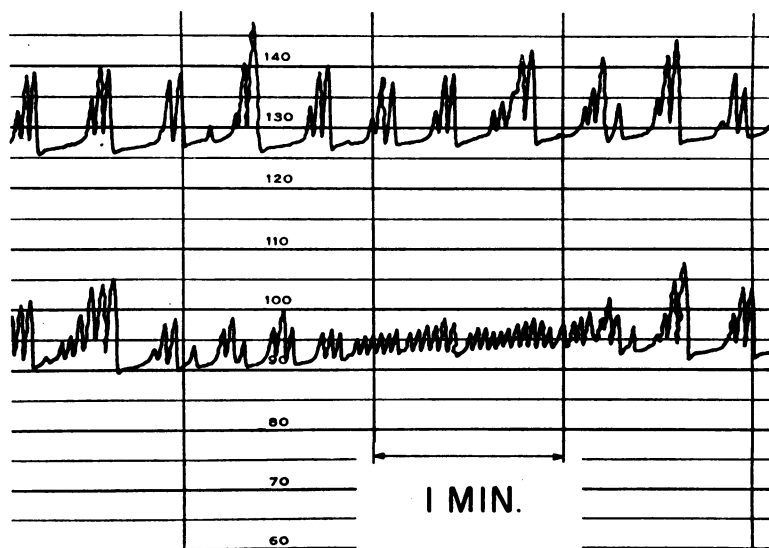


FIG. 4. "CHEYNE-STOKES RESPIRATION" SEEN IN A NORMAL SUBJECT AT SIMULATED ALTITUDE. This ventilatory pattern is from a normal subject, supine, breathing 10 per cent oxygen in nitrogen at a barometric pressure of 630 mm Hg. Note that cyclic respiration (upper tracing) occurs at a higher frequency than in Figures 2 and 3. The cycle period varies between 18 and 22 seconds. At times apnea is not complete. (Continuous spirometer tracing; courtesy Ulrich Luft, M.D.)

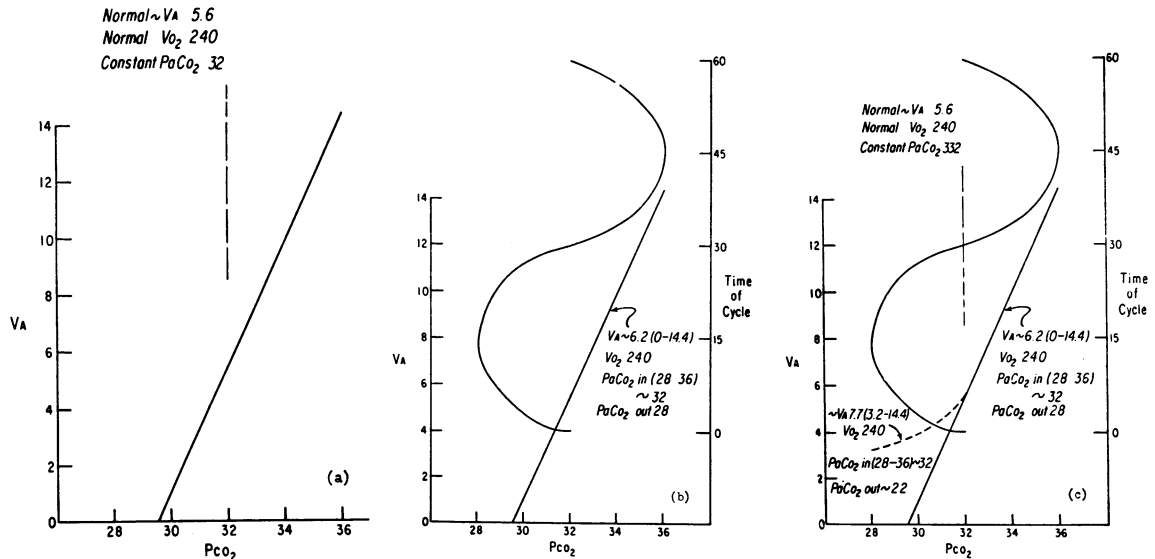


FIG. 5. (a). THE $P_{aCO_2} - V_A$ RELATIONSHIP (18, 20). The slope of the straight line is related to respiratory center sensitivity. Values below 32 are by extrapolation. $R = 0.8$, $V_{O_2} = 240$, $V_A = 5.6$, $P_{aCO_2} = 32$. Input = output.

(b) Added to (a) is a sinusoidal line indicating the time course of P_{aCO_2} found in phasic breathing with a period of 60 seconds (ordinate on right). At any instant the intercept of a vertical from the sine curve to the straight line would give the expected level of ventilatory activity. Note that no positive intercept exists between 5 and 25 seconds (apnea). Instantaneous ventilation over the entire cycle ranges from 0 to 14 L per minute. The mean level of V_A is 6.2. R would vary during the cycle. A mean P_{aCO_2} input of 32 (range 28–36) would result in an “open-loop” output of 28 mm Hg.

(c) In addition to (b), a first approximation is made to the effective gas exchange during the apneic phase. This results in a mean “open-loop” output of 22 in response to a mean input of 32.

sents the respiratory control system rendered unstable primarily by an increase in gain of the amplifier component. This increase in gain would be due to the additive or synergistic effects of hypoxia. Again the frequency of oscillation would be fixed by the transit time of the feedback signal.

The foregoing assumptions have implied a normal response of respiratory center(s) to variations in blood gases. However, the mild to moderate hypocapnea which has been observed has led to the suggestion that there may be a primary respiratory mechanism that causes cyclic respiration, with hyperexcitability of the center(s) causing intermittent hypocapnea and apnea. One should recall that a mild degree of hypocapnea is found in individuals with chronic circulatory impairment associated with pulmonary venous congestion (18). Since congestive heart failure of some degree with increased pulmonary venous pressure was the hallmark of the patients in the present study, one would expect a lowered average P_{aCO_2} in these patients even if cyclic respiration were not present. Table IV indicates, however,

that the degree of hypocapnea in C-S respiration in this and other studies is greater than that found in patients with severe, chronic elevation of the pulmonary venous pressure alone. For this reason further description of the respiratory center function is needed.

Figures 2 and 3 show a near sine wave variation in Sa_{O_2} . This is accompanied by variation in P_{aCO_2} which follows a similar but reciprocal relation. This results in a sinusoidal phasic variation of P_{aCO_2} which acts as a stimulus to the respiratory center. The specific effects of such phasic variations are unknown and have not been considered. The response of the intact respiratory control system to a step input increase in P_{iCO_2} is known, but the difficulty of producing oscillatory variation in stimuli in a normal individual limits specific investigation. One must exercise caution in attempting the use of “steady state” observations in explaining transient phenomena (7).

Information exists, however, regarding the steady state relations between P_{aCO_2} and alveolar ventilation in normal individuals as the P_{iCO_2} is

varied (18, 20). When plotting ventilation as an ordinal value, a nearly linear relationship with P_{aCO_2} is seen (Figure 5a). If this P_{aCO_2} -VA line is extrapolated to values of P_{aCO_2} lower than those found with resting control ventilation of 32, a positive intercept on x is found.

Although sea-level studies can not be rigorously translated to ambient altitudes, for the purpose of this discussion the sea level P_{aCO_2} -VA curve has been translated along the x axis so that the control ratios become those found in normal individuals at this altitude (4,500 feet) (VA 5.6 L per minute; P_{aCO_2} 32 mm Hg). Although the slope of the ventilation-arterial tension curve, as shown, may differ slightly from that seen at sea level, the conclusions to be drawn are relatively insensitive to the absolute value of the slope. From Figure 5a progressive reduction of P_{aCO_2} should cause cessation of ventilation at 29.5 mm Hg. In the upper part of 5b a sine wave variation of P_{aCO_2} is plotted with a period of 60 seconds and an amplitude (8 mm Hg) which might be found in C-S respiration. The summation at 60 1-second intervals of instantaneous ventilation, calculated from the intercept of the sine wave P_{aCO_2} with the P_{CO_2} ventilation line, allows an estimation of mean ventilation over the entire cycle. If the sinusoidal variation in P_{aCO_2} is such that it exceeds the theoretical "cut-off point" for a significant portion of the cycle, the average ventilation resulting from a fluctuating CO_2 level would be higher than the ventilatory response expected for a constant P_{aCO_2} . This indeed was the case with a mean VA of 6.2 (range 0 to 14.4) and resulted in a decrease in P_{aCO_2} and P_{aCO_2} of the constantly perfusing blood (to a mean value of 28 mm Hg).

Since perfusion continues during apnea one should remember that, despite cessation of external ventilation, "effective" ventilation is maintained for 15 to 20 seconds, particularly if the subject is at rest and the lung was well ventilated previous to the apnea. This factor appears in the composite figure (5c) as the dashed, curvilinear line extending down from the resting point. It is considered a first approximation of an arbitrary "effective ventilation" line representing the gas exchange during the apneic period. When this line is used to calculate mean alveolar ventilation with the same sinusoidal input, the deviation of

mean ventilation from the control is even more striking. The mean VA now becomes 7.7 (range 3.2 to 14.4) with a mean P_{aCO_2} and P_{aCO_2} of 22 mm Hg. These considerations do not include the effects of feedback and therefore we have described an "open-loop response."

The full deviation (or open-loop response) would of course not be seen, because the resulting negative feedback would quickly alter the sinusoidal input curve. Although compensatory mechanisms would minimize the effects of the asymmetrical response, these considerations serve to show the direction and approximate magnitude of the effects of sinusoidal variation of P_{aCO_2} . A sinusoidal variation of P_{aCO_2} of greater than 3 mm amplitude would therefore serve to decrease the mean arterial P_{CO_2} , because the effect of hyperventilation at the height of P_{aCO_2} is incompletely compensated during the apneic phase. This is attributable both to the location of the apneic intercept and to the persistence of gas exchange in the absence of external ventilatory activity. One would expect, furthermore, that for a given respiratory sensitivity to P_{CO_2} in an individual in whom the level of P_{aCO_2} varied in such a manner, the mean P_{aCO_2} would be lower than in the same individual when the arterial CO_2 tension was nearly constant. We conclude that the finding of a mild to moderate hypocapnea does not necessarily indicate an increase in sensitivity of the respiratory center to the partial pressure of CO_2 . It is difficult to quantify the effects of the cyclical variations of P_{aCO_2} seen in a given patient, but there exists fair agreement between the observed deviation of the mean P_{aCO_2} seen in these patients (27.2 vs 32 for normal male subjects studied in the same laboratory) and the theoretical deviation calculated from a sine wave input with an 8 mm Hg amplitude. The observed amplitude ranged from 3 to 11 mm Hg (Table III).

Hypocapnea in the presence of congestive heart failure is not unexpected, particularly when pulmonary congestion is present. Table IV indicates that the cases of Pryor (3) and those reported here show mean levels of P_{aCO_2} which deviate from the normal values somewhat more than do the levels of P_{aCO_2} in patients with severe mitral stenosis (17).

An explanation for hypocapnea in the case of

TABLE IV
Hypocapnea found with heart disease with and without Cheyne-Stokes respiration

	Normal	Cheyne-Stokes resp.	Severe mitral stenosis
Paco ₂			
Sea level	39*	32†	36‡
Salt Lake City (4,200 ft)	32	27	

* Ref. 19; † Ref. 3; ‡ Ref. 18.

gross heart failure and C-S respiration would not require any particular alteration in the function of the respiratory center but could be related to both the increased afferent stimuli from pulmonary receptors and the above mechanisms. In the case of C-S respiration in the absence of gross failure or pulmonary congestion, the peculiar effects of cyclical variation of PaCO₂ alone could account for the observed decrease of PaCO₂. Indeed, the usual application of increased P_ICO₂ for the measurement of "respiratory center sensitivity" would seem invalid in cyclic respiration.

SUMMARY

1. Continuous simultaneous measurements of arterial blood gas values and ventilation were made on nine patients with Cheyne-Stokes (C-S) respiration on the medical service of a general hospital.

2. Eight of nine patients were males, over the age of 59, and all had heart disease. Three had definite cerebrovascular disease.

3. The physiological abnormalities observed consistently included phasic shift between the cyclic variation in alveolar and arterial gas values, prolonged circulation time (lung to artery), normal SaO₂ in the absence of recent pulmonary edema, and hypocapnea.

4. The altered physiological parameters were compared with appropriate analogies in physical systems. When viewed in this manner the observations support the theoretical assumption that the basic mechanism for C-S respiration lies in the prolonged lung-to-brain circulation time and the loss of effective damping factors. The respiratory center acts appropriately. When C-S respiration is induced in normal subjects by means of in-

creasing sensitivity to CO₂, the cycle period is related to circulatory delay as in the patients reported here.

5. The consistent finding of hypocapnea may be explained partially on the basis of congestive heart failure (when present) or on the peculiar effects of cyclic variation of PaO₂ on a respiratory center which, because of its nonlinear response, will cause increased mean alveolar ventilation if the amplitude of cyclical variation of PaCO₂ is such that the PaCO₂ falls below the apneic point on its downward excursion. The latter theoretical possibility is explored by means of available data. Such semiquantitative treatment yields results which fit the observed depression of the average PaCO₂ without involving "hypersensitivity" of the respiratory center.

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