Cardiac Arrhythmias Associated with Cheyne-Stokes Respiration: A Note on the Possible Mechanisms*

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Cardiac arrhythmias consisting of A-V block of varying grades have been observed fairly frequently by us in patients with Cheyne-Stokes respiration secondary to left ventricular failure. Nine patients with Cheyne-Stokes respiration (CSR) related arrhythmias and five with little or no irregularity during CSR were studied in the hope of elucidating the responsible mechanisms. Arterial and cerebrospinal fluid gas tensions, arterial and cerebral venous pressures and CSF pressures were recorded continuously. The slowing of heart rate and true A-V block which occurs at the end of apnea or early hyperpnea were found to be purely vagal in nature and correctable with atropine. The most likely factors seem to be variations in arterial blood gases, and perhaps more importantly, of cerebrospinal fluid $P_{CO_2}$ and pH. It is postulated that cardio-regulatory centers similar to respiratory centers may be scattered on the surface of medulla and respond to changes in CSF gas tensions.

Cyclic variations in heart rate and rhythm related to periodic breathing were first noted by Traube1 in 1871 and have since been the subject of numerous studies.2-26 The responsible mechanisms, however, have not been sufficiently elucidated. Though the presence of an increased vagal tone usually brought about by digitalis has been agreed upon by nearly all workers, no convincing explanation for its fluctuations leading to cyclic cardiac arrhythmias has been advanced. The purpose of this communication is twofold, first to call attention to the interesting and sometimes confusing cardiac rhythm disturbances that we have observed in Cheyne-Stokes respiration (CSR) over the past five years, and second, to report on the phasic fluctuations in the hemodynamic phenomena in blood gas tensions and in cerebrospinal fluid (CSF) pressure and gas tensions which occur in unison with CSR cycles and may be operative in the genesis of cardiac arrhythmias.

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MATERIALS AND METHODS

Only patients with classic crescendo-decrescendo type of periodic breathing separated by periods of apnea were studied. Special parameters of blood and CSF gas tensions and pressures were possible in only 14 of the total 41 cases taken under intensive clinical, electrocardiographic and respiratory observations over the past five years. Of these 14 patients nine had unquestionable CSR-related cyclic cardiac arrhythmias (Cases 1 through 9, Group A) and five had CSR without significant cyclic variations of rhythm (Cases 10 through 14, Group B). The cause of CSR was left or biventricular failure in all, and return of cardiac competence was invariably associated with disappearance of CSR. The majority of the patients were receiving digitalis at the time of the study. Table 1 presents biographic and clinical data in both groups.

The plan of investigation was to study first the magnitude and nature of cyclic changes in arterial, venous and CSF dynamics and gas tensions, and to seek possible correlations. The special studies included continuous recordings over many CSR cycles of: 1) respiration (pneumonogram); 2) electrocardiogram; 3) arterial and CSF pressures; 4) pressures from internal jugular vein or intracranial venous sinuses approached by an internal jugular vein catheter or, by retroauricular needle puncture, and 5) hydrogen, oxygen, and $CO_2$ tensions in the arterial and internal jugular venous blood and the CSF in as many cases as feasible. When possible, samples were drawn in early, middle and late phases of both apnea and hyperpnea. Duplicate measurements were not always possible to obtain because of the nature of the study requiring the samples to be drawn in quick succession during a single CSR cycle.
The response of the respiratory and cardiac periodicity to various pharmacologic agents was determined and the effect on cardiac arrhythmia of abolition of respiratory periodicity was studied. Intravenous atropine (1 mg) was used to eliminate the vagal effect without altering the respiratory pattern while voluntary hyperventilation was employed for the purpose of eliminating the periodicity of breathing. It was not possible to complete all the projected studies in every case (Table 2). All the patients required cardiac catheterization and spinal tap for diagnostic purposes and the present studies were included after patients’ consents had been secured.

Electrocardiograms, simultaneous pneumograms and pressures were recorded on a photographic Electronics-for-Medicine DR-8 recorder. Statham P 23Db transducers were used for all pressures. Blood and CSF gas tensions were measured with an Instrumentation Laboratories’ gas analyzer.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Clinical Diagnosis</th>
<th>Cardiac Failure w/CSR</th>
<th>Arrhyth. Assoc. w/CSR</th>
<th>Heart Rhythm &amp; Rate/min. Dur. Apnea</th>
<th>Heart Rhythm &amp; Rate/min. Dur. Hyperpnea</th>
<th>Digitalis</th>
<th>Post Mortem Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>M</td>
<td>Primary myocardial disease, CHF</td>
<td>Acute and chronic</td>
<td>Yes</td>
<td>Sinus tachy. 1° AV block 100</td>
<td>2° Heart block PVC’s A = 62. V = 38.</td>
<td>Toxicity</td>
<td>Card. dil. fibrosis</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>F</td>
<td>Diab. mell., malignant hypertension, LV failure</td>
<td>Acute</td>
<td>Yes</td>
<td>N.S.R. 1° AV block 78</td>
<td>2° Heart block A = 68. V = 62.</td>
<td>Yes</td>
<td>—</td>
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<tr>
<td>3</td>
<td>62</td>
<td>F</td>
<td>Obesity, card. pulm. syndr., ASHD</td>
<td>Acute</td>
<td>Yes</td>
<td>Sinus tachy. 120</td>
<td>Sinus brady. to sinus arrest A = 0–50. V = 30–50.</td>
<td>No</td>
<td>Cor. ascl. pneumonia bronchial tasis cer. ascl.</td>
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<td>5</td>
<td>80</td>
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<td>Abdo. aneur., hypertension, CHF</td>
<td>Chronic</td>
<td>Yes</td>
<td>N.S.R. 70</td>
<td>Sinus brady. &amp; sinus arrest 40</td>
<td>Toxicity</td>
<td>—</td>
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<tr>
<td>6</td>
<td>71</td>
<td>F</td>
<td>Ao. stenosis, Insuffic., CHF</td>
<td>Acute and chronic</td>
<td>Yes</td>
<td>Atrial fibr. V = 70–90.</td>
<td>Atrial fibr. V = 55–75.</td>
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<td>Aortic sten., pulm. emboli</td>
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<td>M</td>
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<td>Acute and chronic</td>
<td>Yes</td>
<td>Sinus tachy. 2–1 AV block A = 120. V = 56.</td>
<td>Sinus tachy. 1° AV block A = 120. V = 122.</td>
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<tr>
<td>8</td>
<td>85</td>
<td>F</td>
<td>ASHD, CHF</td>
<td>Chronic</td>
<td>Yes</td>
<td>N.S.R. LBBB 1° AV block</td>
<td>Wenckebach phenomenon 60–72 Normal QRS</td>
<td>Toxicity</td>
<td>—</td>
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<tr>
<td>9</td>
<td>68</td>
<td>M</td>
<td>Chronic heart block—CHF</td>
<td>Chronic</td>
<td>Yes</td>
<td>AV block nodal escape RBBB V = 40–50/min.</td>
<td>AV block nodal escape LBBB V = 58/min.</td>
<td>Yes</td>
<td>—</td>
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<tr>
<td>10</td>
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<td>F</td>
<td>Hypertension, acute cere. hemorrhage CHF</td>
<td>Chronic</td>
<td>No</td>
<td>Atrial fibr. PVC’s V = 76</td>
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<td>Toxicity</td>
<td>—</td>
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<tr>
<td>11</td>
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<td>Diab. mell. ASHD, CHF cere. thromb.</td>
<td>Chronic</td>
<td>No</td>
<td>Atrioventr. dissoci. V = 60</td>
<td>Atrioventr. dissoci. V = 56</td>
<td>Toxicity</td>
<td>—</td>
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<td>Posterior MI, hypertension CHF</td>
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<td>N.S.R. 78</td>
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<td>13</td>
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<td>Cer. thromb. ASHD, CHF</td>
<td>Chronic</td>
<td>No</td>
<td>Sinus tachy. 114</td>
<td>Sinus tachy. 114</td>
<td>Yes</td>
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<tr>
<td>14</td>
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<td>M</td>
<td>ASHD, cere. thromb. CHF</td>
<td>Chronic</td>
<td>No</td>
<td>N.S.R. 86</td>
<td>N.S.R. 84</td>
<td>Yes</td>
<td>Died. No PM</td>
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</table>


In this patient, the pattern of arrhythmia was opposite that found in all other cases in that AV conduction was impaired during apnea and enhanced during hyperpnea.
RESULTS

Considerable changes in cardiac rate and rhythm occurred from apnea to hyperpnea (Table 1). The rate was in general more rapid and regular during apnea and slower and more irregular during hyperpnea, with the greatest change occurring either near the end of apnea or the beginning of hyperpnea. In Group A where the cardiac rhythm fluctuations were significant, the slowing of the rate was caused by sinus bradycardia and/or sinus arrest in two cases, progression of heart block from first degree to second degree in three cases, slowing from 40–50/min to 28/min of the ventricular rate in the face of complete AV block in one, development of a slow ventricular rate in the presence of AV dissociation in one and slowing of ventricular rate in atrial fibrillation in one patient. Case 7 was unusual in that slowing occurred during the apnea phase and was caused by the development of 2–1 AV block in the face of a fixed sinus tachycardia.

Arterial and Cerebral Venous Gas Tensions: Arterial and cerebral venous blood O₂ and CO₂ tensions (P₀₂, P₀₂) in both Groups A and B are presented in Table 2 and Figure 1. The P₀₂ values recorded under columns A and H of Table 2 represent averages of several random samples drawn during apnea and hyperpnea of several consecutive CSR cycles. In only six patients was it possible to draw six samples during a single CSR cycle and the resultant values are depicted in Figure 1. In general, the P₀₂ values were lower and P₀₂ values higher during hyperpnea than in apnea. This inverse relationship of P₀₂ and P₀₂ incriminates

\[ P₀₂ = \frac{P₀₂}{P₀₂} \]

Figure 1. Arterial carbon dioxide tension (P₀₂), oxygen tension (P₀₂) and cerebral venous oxygen tension in six cases (Cases 1, 2, 3, 6, 12, 13) in which it was possible to obtain six samples during a single CSR cycle corresponding to early, middle and late portions of apnea and hyperpnea (A₁, A₂, A₃, H₁, H₂, H₃). Note that P₀₂ was considerably higher in apnea than in hyperpnea and that the rate of change was steepest between the middle and late apnea, i.e. the time of greatest rhythm change. P₀₂ remained relatively constant and of a low magnitude suggesting a persistent cerebral hypoxia. P₀₂ which was quite variable in its level followed a pattern opposite that of P₀₂. Here too, the steepest rise was between mid and late apnea thus corresponding to the time of greatest rhythm change.

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alveolar ventilation as the basic mechanism for blood gas alterations. The apparently paradoxical relationship of arterial blood gases to the pattern of breathing is easily explained on the basis of the markedly prolonged lung-artery circulation time. That is to say, the gas exchange taking place at the alveolo-capillary level is depicted in the peripheral arteries after a lapse of as many seconds as it takes the pulmonary capillary blood to reach the peripheral arteries. Since this period may be as long as 25 to 30 seconds in the presence of left ventricular failure, the alveolo-capillary events of the apnea phase may not be detectable in the peripheral arteries until the next hyperpnea. The data in Figure 1 are of particular interest because they demonstrate the behavior of blood gas tensions within the various segments of a given phase of CSR. The rate of change of PaO2 and PaO2O2 are shown to be greater during apnea than hyperpnea and the time of steepest change is found to be between mid-apnea, and late apnea, thus corresponding to the time of greatest rhythm change. It is noted, however, that the simultaneously drawn cerebral venous blood samples exhibit much less steep fluctuations in Po2, with the result that changes in cerebral AV Po2 difference are chiefly accounted for by the variations in arterial Po2. The very low and almost constant cerebral venous Po2 suggests a constant cerebral hypoxia with maximal O2 extraction irrespective of the arterial Po2.

Arterial and Cerebral Venous Pressures: Nine subjects with intracranial venous pressure measurements demonstrated an average rise in mean venous pressure during hyperpnea of 4 mmHg with the elevation beginning five to ten seconds after the onset of hyperpnea (Table 2, Fig 2 and 3). The arterial pressure rose modestly during late hyperpnea in five cases. Case 3, on the other hand, exhibited a highly exaggerated arterial pressure response with striking fall during hyperpnea coincident with slowing of the heart rate (Fig 4). Both the arrhythmia and the fall in blood pressure were abolished with atropine notwithstanding the persistence of the CSR and were clearly due to fluctuations in the vagal tone.

CSF Gas Tensions: Depicted in Table 3 are CSF gas tensions which could be measured in only eight cases. Considerable variations were observed in both Po2 and pH with the largest fluctuations found between samples obtained during mid apnea and those of end apnea (Fig 5). This is of particular interest because the greatest change in the cardiac mechanism was also observed at this point of the CSR cycles. In Case 7 in whom the pattern of arrhythmia was in reverse order the CSF gas tensions changed in a direction opposite that of all other cases.

CSF Pressure: This was measured in the same eight cases as those of Table 3. Striking fluctuations from apnea to hyperpnea were observed in all. The
pressure was invariably higher during hyperpnea and the magnitude of rise of the mean pressure was as high as 15 mmHg in one case and over 5 mmHg in seven. The mean value for the rise of CSF pressure from apneic to hyperpneic was 8 mmHg (Table 2, Fig 2, 3).

![Figure 4](case5.jpg)

**Figure 4 (Case 5).** Simultaneous recording of pneumonogram, brachial arterial pressure, internal jugular venous pressure and ECG. The recording of internal jugular venous pressure is interrupted just to the left of the center when the stop cock was turned around for intravenous atropine injection. Note the striking pressure fluctuations with a precipitous fall in early apnea coincident with marked slowing of heart rate. Atropine abolished the arrhythmia and stabilized the blood pressure indicating the primary role of the vagus in the genesis of both arrhythmia and blood pressure fluctuations. In this case, the jugular venous pressure displayed larger swings during hyperpnea, but did not rise in its mean value.

**Case Reports**

**Case 1:**

A 65-year-old man with chronic biventricular failure of four years' duration secondary to primary myocardial disease was admitted to the hospital in failure and CSR on July 13, 1964. He had been receiving 0.5 mg digoxin daily.

A routine electrocardiogram showed seemingly spontaneous variations in rate and rhythm from one lead to another. Continuous electrocardiographic monitoring later on that day demonstrated periods of bradycardia due to

![Figure 5](case3.jpg)

**Figure 5.** Cerebrospinal fluid, $P_{CO_2}$ and pH values obtained four times in sequence during the same CSR cycle in eight patients (Table 3). $A_2$, $A_3$, $H_2$ and $H_3$ refer to middle and late portions of apneic and hyperpneic respectively. Note the steep fall in $P_{CO_2}$ and the steep rise in pH in samples from middle to late apnea, while the change was less pronounced in other samples. The coincidence of the steep changes in CSF gas tensions with the time of greatest rhythm change is impressive. Case 4 is of particular interest in that changes in CSF gas tensions occurred in a direction opposite all other cases and the pattern of his arrhythmia was also reversed. Numbers 1 to 8 refer to cases as they appear in Table 3.

![Figure 6](case1.jpg)

**Figure 6 (Case 1).** Simultaneous ECG and pneumonogram recorded at 10 mm/sec in top strip "a" and at 25 mm/sec in strips "b" and "c". The slowing of heart rate begins in late apnea and reaches its peak in early hyperpnea. The exact mechanism is shown in strip "b" to be one of gradual slowing of the sinus rate associated with prolongation of the PR interval which in turn culminates in second degree AV block. The simultaneous occurrence of slowing of the sinus pacemaker with prolongation of the PR indicates vagal action.
second-degree heart block (Fig 6). Careful observation revealed that the AV block was preceded by a slowing of the sinus rate, thus indicating interaction of the vagus. Further monitoring with the aid of a simultaneously recorded pneumonogram during several CSR cycles revealed a constant relationship between cardiac rate and respiratory cycles where a progressive sinus slowing began in late apnea and culminated in second-degree AV block in early hyperpnea. Sinus tachycardia returned in late hyperpnea (Fig 6). Carotid sinus stimulation during early apnea was capable of precipitating both sinus slowing and AV block and thus reproducing the events observed spontaneously during late apnea. Administration of intravenous atropine abolished the arrhythmia without affecting the respiratory pattern (Fig 7A and B). Voluntary hyperventilation or hyperpnea produced by inhalation of 5 per cent CO₂ abolished the cardiac arrhythmia (Fig 8).

Digoxin was withheld and atropine was given intramuscularly at a dosage of 0.4 mg every six hours for six days. Although the CSR persisted, the arrhythmia disappeared in two days and could no longer be elicited by carotid sinus stimulation. However, the administration of ouabain 0.25 mg intravenously six days later did result in a reappearance of AV block during early hyperpnea (Fig 7C). The CSR and the cardiac arrhythmia became progressively less striking and eventually disappeared as cardiac function improved. Periodic breathing associated with similar arrhythmias was also noted on his final admission for heart failure in September, 1964. Post-mortem examination demonstrated marked cardiac hypertrophy and dilation, diffuse myocardial fibrosis and severe congestion of the viscera. For blood and CSF data, see Tables 2 and 3 (Fig 1 and 5).

**Comment:** In this case of CSR associated with heart failure, an advanced degree of AV block occurred during late apnea and early hyperpnea. This was preceded by a gradual slowing of the sinus rate. The central role of the vagus in the genesis of this arrhythmia was demonstrated both through atrioventricular and carotid sinus stimulation. The reappearance of CSR-related arrhythmia after administration of ouabain at a time when the initial arrhythmia had ceased demonstrated the role of digitalis. The importance of respiratory periodicity was pointed out by the disappearance of arrhythmia during voluntary hyperventilation and CO₂ inhalation. Of particular interest was the wide fluctuations in the CSF CO₂ tension with the greatest change (48 to 42 mmHg) occurring between the samples obtained at the middle and end of apnea coinciding with the time of greatest rhythm change.

**CASE 2:**
A 33-year-old woman with hypertension was admitted on July 28, 1964, because of progressive left ventricular failure. She was receiving oral digoxin 0.25 mg daily and was given 1.0 mg of this drug intravenously after admission. Three days later, an electrocardiogram demonstrated an arrhythmia which, on subsequent monitoring, was found to be due to a second-degree AV block beginning at the end of apnea and returning to regular sinus rhythm at the end of hyperpnea (Fig 9A and B). This arrhythmia could be reproduced at will at any selected part of the CSR cycle by carotid sinus massage and totally abolished by intravenous atropine. Voluntary hyperventilation also abolished the AV block. Both the CSR and the cardiac arrhythmia disappeared after failure subsided.

**Comment:** As in Case 1, the CSR accompanying cardiac failure was associated with severe cardiac arrhythmia which was clearly related to a heightenened vagal tone during late apnea and early hyperpnea. Again, the role of respiratory periodicity was demonstrated.

**CASE 3:**
A 62-year-old obese woman presented in congestive heart failure following recent respiratory infection. She was febrile, lethargic and exhibited CSR. The admission electrocardiogram and subsequent monitoring of respiration demonstrated a CSR-related arrhythmia characterized by sinus tachycardia during apnea and slowing of the rate and eventually sinus arrest and a slow nodal rhythm beginning in late apnea (Fig 9, C and D). The arrhythmia was completely abolished by atropine. Pressures in the internal jugular vein and the CSF were considerably higher during hyperpnea than in apnea (Fig 2).

**Comment:** A vagally mediated sinus bradycardia and even sinus arrest occurred in this case toward the end of apnea and early hyperpnea in the absence of digitalis. The CSF pressure rose considerably during hyperpnea.
striking with a rise in mean pressure during hyperpnea of 15 mm Hg (Fig 3). The CSF gas tensions showed the greatest change from the middle to the end of apnea (Table 3).

**Comment:** In this case, AV dissociation apparently related to digitalis, was affected by CSR. Both atrial and ventricular rates decreased in late apnea and early hyperpnea. The hyperpneic rise in CSF pressure was most pronounced and changes of gas tensions in CSF were steepest from mid to end apnea corresponding to the time of cardiac slowing.
CASE 5:

An 80-year-old woman with known hypertension was admitted to the hospital because of progressive cerebral vascular insufficiency and signs of left ventricular failure. The admission electrocardiogram demonstrated normal sinus rhythm. Reserpine (0.25 mg twice daily) was started and 2.0 mg digoxin were given by mouth during the first 36 hours. Two days after admission, she was anorectic and nauseated and her ECG showed a supraventricular tachycardia. Digoxin was withheld, and on the following day she was noted to have CSR and a phasic sinus arrhythmia. ECG monitoring demonstrated the occurrence of marked sinus bradycardia with wandering pacemaker and short periods of sinus arrest at the end of apnea and at the onset of hyperpnea.

The arrhythmia could be reproduced at any time in the respiratory cycle by carotid sinus stimulation. Intravenous atropine as well as voluntary hyperventilation abolished both the naturally occurring and carotid sinus-induced forms of the arrhythmia. Of great interest was the striking fluctuations observed in the arterial pressure coincident with phasic fluctuations in pulse rate (Fig 4). The pressure reached 192/84 mm Hg and pulse rate became as slow as 40/min during hyperpnea. The respective values for apnea were 130/92 and 70. Fluctuations in internal jugular venous pressure were modest. Arterial pressure variations ceased to occur when the vagal activity was abolished by atropine (Fig 4). On the following day, although CSR persisted, no arrhythmia was present until intravenous ouabain (0.4 mg) was given and the carotid sinus was stimulated.

Comment: The mediating role of digitalis and of the vagus in the production of cardiac arrhythmia were demonstrated by the reappearance of arrhythmia after ouabain administration and the characteristic response to atropine injection and to carotid sinus stimulation. The marked fall of the arterial pressure during hyperpnea notwithstanding the slowing of heart rate incriminated vagal interaction.

CASE 8:

An 85-year-old woman who had been receiving digitalis leaf 0.1 mg daily for several years was admitted in severe congestive heart failure and marked CSR. Her pulse rate was regular at a rate of about 104/min in early and mid-apnea and slowed to about 60/min at the end of apnea and early hyperpnea. Electrocardiograms (Fig 10) with marking of breaths showed sinus tachycardia with marked prolongation of the PR intervals to 0.30 sec in early mid-apnea. Toward the end of the apnea phase the sinus discharge slowed gradually and the PR intervals became longer and finally one blocked P occurred. The beat following this long cycle displayed normal intraventricular conduction while all the other beats preceded by shorter cycles showed left bundle branch block. The CSF gas tensions showed steep changes from mid to end apnea (Table 3).

Comment: This was a case of CSR-related arrhythmia in which second-degree AV block and slowing of the heart rate occurred in early hyperpnea. Of further interest was the normalization of intraventricular conduction when the heart rate became slower than 60 beats/min. The temporal relation-ship of the arrhythmia with the steep fall in CSF, \( p_{co2} \) and rise in pH is again intriguing. Bilateral bundle branch block may also explain the arrhythmia in this case.

Table 3—Cerebrospinal Fluid Gas Tensions in Eight Cases

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Mid Apnea</th>
<th>End Apnea</th>
<th>Mid Hyperpnea</th>
<th>End Hyperpnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pCO&lt;sub&gt;2&lt;/sub&gt; 48</td>
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<td>43</td>
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<tr>
<td></td>
<td>pH 7.39</td>
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<td>7.39</td>
<td>7.44</td>
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<td>40</td>
<td>41</td>
<td>45</td>
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<td></td>
<td>pH 7.29</td>
<td>7.34</td>
<td>7.27</td>
<td>7.32</td>
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<tr>
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<td>48</td>
<td>49</td>
<td>51</td>
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<td></td>
<td>pH 7.29</td>
<td>7.34</td>
<td>7.30</td>
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<td>pH 7.40</td>
<td>7.44</td>
<td>7.38</td>
<td>7.36</td>
</tr>
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</table>

Means pCO<sub>2</sub> 45.3 39.0 42.1 44.3

\( \Delta \) = differences between values obtained in the 4 phases of CSR cycles.

Application of the trend changes was opposite in this patient to all others. For this unexplained reason, his values are not included in the computation of the means.

\( \Delta = \) differences between values obtained in the 4 phases of CSR cycles.

Comment: In this case of complete heart block with failure caused by cessation of artificial pacing by the pacemaker seemed to reside in the AV junctional tissue whose rate of discharge was affected markedly by fluctuations of the vagal tone brought about by CSR. The alternating left and right bundle branch block represented either a bilateral bundle branch block or a form of rate dependency and intraventricular conduction defect in which slower rates favored block of the left, while faster rates unearthed block of the right bundle branch. Acceleration of the rate by atropine eliminated the bradycardia-dependent block of the left bundle.

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FIGURE 10 (Case 8). Sequential recording of V₁ during three CSR cycles showing a change from first degree AV block with sinus tachycardia and left bundle branch block in apnea to one of second degree AV block with disappearance of left bundle branch block in hyperpnea. The emergence of second degree AV block was preceded by a gradual slowing of the sinus pacemaker, again indicating the role of vagal tone (see beats 12 to 17, Row A and 33 to 38, Row B with RR intervals marked in 0.01 sec).

branch. The coincidence of the slowing of heart rate with the steep fall in CSF, Pₐ₀₂ and rise in pH was again noted.

 DISCUSSION

The present study has made it abundantly clear that the CSR-related cyclic cardiac arrhythmia depends on the intimate interaction of respiratory periodicity and an increased vagal tone. Neither factor alone was found to be sufficient to cause changes in cardiac rate and rhythm.

A brief review of the various mechanisms thought to be responsible for periodicity of breathing in CSR suggests that none could singly account for the accompanying fluctuation in cardiac mechanism. Thus, the early concept of hypersensitivity of the cells of the respiratory center to carbonic acid secondary to an accumulation there of lactic acid at the end of apnea, championed by Douglass and Haldane was soon challenged by Anthony and Cohn and later proved to be erroneous when Pryor demonstrated in 1951 that, paradoxically.

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enough, the maximal hypoxemia was present at the end of hyperpnea and not the end of apnea as had been supposed over the preceding 40 years. Pryor suggested the mechanism to be the delay in transmission of messages from the alveolo-capillary level to the respiratory center brought about by the prolonged lung-to-artery circulation time consequent upon left ventricular failure. Experimental demonstration of this concept was provided by Guyton et al. in 1956 when they produced CSR by experimentally lengthening the carotid arteries and delaying arrival of the blood from the pulmonary capillaries to the respiratory center. Other notable studies pointing out the importance of prolonged lung-artery circulation time are those of Altschule and Ingla2r and Lange and Hecht.

In the latter study, the length of the respiratory cycles were shown to be roughly twice the lung-to-artery circulation time. By using engineering analogies, the authors concluded that in CSR the servomechanism control of respiration is unstable; and that the prolonged circulation time is probably the most important component contributing to the breakdown of the control mechanism.

The circulatory theory has been challenged by Brown and Plum who favored hyperexcitability of the respiratory center as the basic mechanism for respiratory periodicity. The hyperexcitability theory can in turn be criticized on grounds of: 1) preponderance of cases of the neurologic type of CSR (stroke, brain tumor etc.) in these studies resulting in omission of the much larger group of cases in which CSR is directly related to left ventricular failure;* 2) insufficient consideration accorded cases in which CSR is associated with hypoexcitability of the respiratory center in extreme obesity and in myxedema. It appears, therefore, that in the cardiac variety of CSR with which this presentation is concerned, prolonged lung-artery circulation time is probably the basic physiologic derangement leading to periodicity of breathing. The lack of any detectable effect on the CSR by atropine tends to exonerate the vagus in the genesis of the respiratory irregularity. In contrast, the vagal hyperactivity is a prerequisite to cardiac arrhythmia as first noted by Biot and by Langendorff and has been repeatedly documented since and confirmed in the present study. The contributory role of digitalis in producing a high vagal tone has likewise been a matter of common knowledge for over 50 years and has been amply confirmed in the present work. All of the previously reported patients with CSR-related cardiac arrhythmias were receiving digitalis and in the present larger series 13 out of 14 were so treated and some were even in digitalis toxicity.

Wenckebach's suggestion that the slowing of pulse during hyperpnea is due to the spread of stimuli from the hyperactive respiratory center to the adjacent cardioinhibitory center may be construed as a direct incrimination of the respiratory center in the genesis of cardiac arrhythmia.

Blood gas alterations per se as factors producing arrhythmia must be considered. The concept dates back to Sir Thomas Lewis' demonstration that extreme hypoxia could cause heart block in vagotomized dogs. The criticism of this study was that the hypoxia induced in his experiments was of lethal magnitude and that lesser grades of hypoxia produced by Eyster and Meek and later by Greene and Gilbert caused only sinus bradycardia through vagal stimulation. That hypoxia is present in CSR and its magnitude is greater during hyperpnea has been shown in this study as well as previously. Measurements of cerebral AV PO2 difference in this study demonstrated the existence of severe cerebral hypoxia. Its great magnitude was shown in one patient in whom inhalation of 100 per cent oxygen for three minutes failed to raise cerebral venous PO2. It may be plausible to ascribe a role to cerebral hypoxia for stimulation of an already hyperactive vagus. However, this does not seem justified for the phase of greatest rhythm change (end of apnea) did not always coincide with the time of lowest arterial PO2. Moreover, inhalation of 100 per cent O2 in several patients failed to abolish the cyclic cardiac arrhythmias.

Fluctuations in arterial PO2 and pH must also be considered specially because they are short-lived and therefore uncompensated. There is no convincing evidence that pH or PCO2 fluctuations of the magnitude observed in CSR exert any direct effect on cardiac mechanism or on the specialized conduction tissue of the heart. However, they can alter the vagal tone significantly. Related to cyclic changes of PCO2 and pH are shifts of potassium ion concentration within the cells of the respiratory center. The only pertinent information available in this respect is that which ascribes a vagal potentiating effect to hyperkalemia.

Fluctuations in blood pressure in CSR have been reported and were found in the present study. The observation that the blood pressure and pulse rate fell simultaneously as seen in Figure 4, sug-
gests vagal hyperactivity and therefore adds little to the understanding of the basic mechanisms underlying periodicity of cardiovascular mechanisms. Similarly, fluctuations in intracranial venous pressure appear as an insignificant factor in changing the heart rate because they are of a minor magnitude.

Fluctuations in cerebrospinal fluid (CSF) pressure appear to be considerable and of significant height during hyperpnea as had been observed previously.\textsuperscript{35,45} The time of onset of the rise in CSF pressure and of bradycardia were sufficiently close to suggest a cause-effect relationship. The basis for the rise in CSF pressure during hyperpnea is not known and may be related to an increase in cerebral blood flow in response to the hypercapnia of hyperpnea. Regardless of the mechanism, the rise in CSF pressure is known to stimulate the vagus nerve.\textsuperscript{46} In fact, Kjallquist et al\textsuperscript{47} found fluctuations in pulse rate \textit{pari passu} with the spontaneous variations of CSF pressure in patients with intracranial hypertension. Similarly, experimental elevation of CSF pressure in cats by injection of inert substances within the brain or into the spinal canal gives rise to slowing of the heart.\textsuperscript{48}

Finally, the possible role of fluctuations in CSF, P\textsubscript{CO\textsubscript{2}} and pH as demonstrated in this study are worthy of special consideration and of particular interest in view of the recent findings by Mitchell et al\textsuperscript{49} and Plum\textsuperscript{50} of ready diffusibility of CO\textsubscript{2} across the blood-brain barrier. The concomitance of the steepest change in CSF, P\textsubscript{CO\textsubscript{2}} and pH with the onset of cardiac arrhythmia appears consistent and probably more than coincidence. If, as suggested by the recent work of Mitchell et al\textsuperscript{49}, respiratory chemoreceptors on the exposed surface of the medulla respond to minimal changes in CSF P\textsubscript{CO\textsubscript{2}} and pH, one may be tempted to speculate that there may also be cardiac rhythm centers scattered on the periphery of the medulla and designed to respond to changes in CSF pH of His.

The observations reported here and those of earlier workers make it amply clear that a large number of cardiorespiratory parameters demonstrate periodicity in unison with phases of respiration in CSR, and that the very multiplicity of factors makes it extremely difficult if not impossible to ascertain the precise cause of cyclic cardiac arrhythmias.

In the present investigation it has been possible to single out the factors that appear most probably responsible for fluctuations in cardiac rhythmicity either directly or through an influence on the vagal tone.

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6 Segala, L.: These de Paris, 1908 (cited by Gallavardin, ref. 9).


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