Pattern of discharge of respiratory neurons during systemic vasomotor waves

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INTRODUCTION

Systemic blood pressure oscillations, produced in paralyzed dogs by arresting ventilation or by hemorrhage during mechanical ventilation, were related to the phasic phrenic nerve electrical activity. Oscillations synchronous with each burst of phrenic nerve activity ("Traube-Hering" waves) occurred in hemorrhaged animals and during arrested ventilation. Oscillations unrelated to the frequency of the phrenic nerve bursts ("Mayer" waves) occurred only after hemorrhage. The integrated activity of each phrenic nerve burst was less and the bursts were more frequent during Mayer waves than during Traube-Hering waves. Neither wave pattern was abolished by carotid chemoreceptors or arterial pressure denervation. Maneuvers (vagotomy or arrested ventilation) which slowed the bursts of phrenic nerve activity and increased the electrical activity of each burst converted Mayer to Traube-Hering waves. The reverse changes in phrenic nerve activity and rate (produced by raising body temperature) changed Traube-Hering to Mayer waves. Traube-Hering waves seem to be caused by a direct influence of the phasic activity of respiratory neurons on vasomotor activity. This phasic activity can prevent Mayer waves.

METHODS

Waves in systemic blood pressure were produced either by graded hemorrhage or by arrested ventilation. Phrenic nerve activity was used as a measure of the ventilatory drive since an earlier study had shown that in spontaneously breathing dogs integrated electrical activity recorded from the phrenic nerve is proportional to the tidal volume, and that the frequency of bursts of phrenic activity corresponds to the respiratory frequency (18). Thoracic movements were recorded using a pneumograph. When waves in blood pressure had been produced and became stable, we studied the effects of changing blood gas tensions, of sympathetic blockade, and of denervating the peripheral chemoreceptors and baroreceptors on the pattern of the waves.

Forty-five dogs were studied. Each was anesthetized with pentobarbital injected intravenously (20–30 mg/kg body wt). Spontaneous respiration was then abolished by the intravenous administration of succinylcholine (0.5–1.0 ml) and the dogs were artificially ventilated with a mechanical respirator (Harvard Co., Cambridge, Mass.). Catheters were placed in the renal arteries for the continuous recording of the systemic arterial blood pressure, using Statham transducers (P23Db); blood was also sampled periodically from these catheters. The cervical portion of one phrenic nerve was exposed, bipolar platinum electrodes were positioned on the surface of the nerve, and the discharge in the nerve was continuously recorded using an oscilloscopic recording apparatus (EEP-8 amplifiers, Electronics for Medicine) to monitor the pattern of respiratory neuron activity. The impulses from the phrenic nerve were also rectified electronically (EEP-8 amplifier) to allow integration as previously described (18), thus permitting quantification of the electrical activity associated with each burst of phrenic nerve discharge.

Cyclical variations in systemic blood pressure, presumably vasomotor in origin, have been observed in spontaneously breathing animals under a variety of experimental circumstances (2, 8–10, 12, 15, 21). These waves have been classified as "Traube-Hering" or "Mayer" waves according to their relations to the frequency of breathing (25). Traube-Hering waves, which have usually been produced experimentally by asphyxia, characteristically have the same interval between the swings in blood pressure as between breaths (11, 20) (Fig. 1A). On the other hand, Mayer waves, which usually have been produced experimentally by hemorrhage, characteristically have longer intervals between swings in blood pressure than between breaths (19) (Fig. 1B).

In spontaneously breathing animals, irregularities in tidal volume and frequency often complicate the interpretation of swings in blood pressure. On the other hand, during controlled ventilation, the measured ventilation provides no clue as to how the respiratory center is behaving. The present study was undertaken in order to relate the phasic output from the respiratory center, as indicated by the phrenic discharge, to the two patterns of vasomotor swings in blood pressure, using an index of respiratory activity other than minute ventilation; therefore, the phrenic neurogram was recorded. In order to eliminate the passive effects of spontaneous ventilation on blood pressure, we resorted either to arrested ventilation or to the artificial ventilation of dogs paralyzed with succinylcholine.
Arrested Ventilation

In 15 dogs, artificial respiration was stopped after 10 min of ventilation with 100% oxygen. The airways of the dogs were immediately connected via an endotracheal tube to an oxygen-containing spirometer; systemic blood pressure, phrenic nerve impulses, and thoracic movements were recorded continuously. Waves in blood pressure appeared within 3–6 min after stopping ventilation. Arterial blood gases, sampled at the time that the waves in blood pressure appeared, showed hypercapnia without hypoxemia (Table 1). Except for occasional premature cardiac contractions, there were no cardiac irregularities. After 6.8 min of arrested ventilation (control period), mechanical ventilation was resumed.

Adrenergic blockade. In 9 of these 15 animals, the alpha-adrenergic blocking agent, phenoxybenzamine, was then administered intravenously (5–10 mg/kg of body weight) while the dogs were mechanically ventilated with oxygen. Alpha-adrenergic blockade was considered to have been accomplished if systemic blood pressure either remained unchanged or decreased after 0.5 ml of epinephrine was given intravenously. When the blockade was complete, ventilation was stopped and blood pressure, phrenic nerve activity, and thoracic movements were recorded as during the control period.

Denervation. In the other 6 (of the 15) animals, bilateral denervation of the peripheral chemo- and baroreceptors was completed before testing the effect of arresting ventilation on the blood pressure. To accomplish the denervation, the vagi and the carotid sinus nerves were severed bilaterally in the neck. If phrenic nerve activity failed to increase after the intracarotid injection of either lobeline (20 mg/kg body wt) or potassium cyanide (0.5 ml of a 0.01 dilution), denervation of the chemoreceptors was considered to have been accomplished.

Artificial Ventilation and Hemorrhage

In 30 additional animals, swings in blood pressure were produced by bleeding while artificial ventilation was continued. The animals were hemorrhaged by withdrawing 50–100 ml of blood every 10 min from the femoral artery. This procedure was continued until the mean systemic blood pressure was 60 mm Hg. After each period of hemorrhage, blood pressures, phrenic nerve activity, and thoracic movements were recorded during ventilation with ambient air or with a mixture of either 10% oxygen in nitrogen or of 7% carbon dioxide in air for at least 5 min.

Adrenergic blockade. To produce alpha-adrenergic blockade, phenoxybenzamine was administered intravenously (5–10 mg/kg body wt), following hemorrhage and during the swings in blood pressure.

Denervation. In 6 of the 30 dogs, the carotid sinus nerves were severed bilaterally to study the effects of denervating the carotid chemo- and baroreceptors on Mayer waves while the aortic chemo- and baroreceptors remained intact. In two of those dogs, the vagi were subsequently cut bilaterally.

Interconversion of Traube-Hering and Mayer waves. In hemorrhaged dogs with Mayer waves, the frequency of the bursts of phrenic nerve activity was decreased in two ways: 1) in nine dogs, the vagi were severed bilaterally (leaving the innervation of the carotid chemo- and baroreceptors intact); and 2) in six dogs, artificial ventilation was stopped during Mayer waves produced by hemorrhage (leaving the innervation of both the carotid and the aortic chemo- and baroreceptors intact).

In two hemorrhaged vagotomized dogs with Traube-Hering waves, the frequency of the phrenic nerve bursts was increased by heating the animals with high-resistance tapes wrapped around the torso until their rectal temperatures reached 39 C. The average rectal temperature before heating was 37 C. Plasma expanders (saline and dextan) were infused to maintain blood pressure at the preheating level.

Analytic procedures. The arterial blood samples were analyzed at 37 C for carbon dioxide tension using a Severinghaus electrode, for oxygen using a modified Clark electrode (Instrumentation Laboratory, Cambridge, Mass.), and for pH using a glass electrode (Radiometer, Copenhagen, Denmark) (14).
corresponded to the usual description of Traube-Hering waves. It may be seen, in Fig. 2A, that each phrenic nerve discharge occurred at the trough of the blood pressure wave and was followed by a transient increase in systemic blood pressure; only one phrenic nerve discharge occurred for each oscillation in blood pressure. Periodic variations in intrathoracic pressure could not explain the pressure waves since all spontaneous movement in these animals had been abolished by neuromuscular blockade with succinylcholine.

Adrenergic blockade. In 9 dogs, ventilation was again stopped 1 hr after the administration of the alpha-adrenergic blocking agent, phenoxybenzamine (Table 1). After phenoxybenzamine, the swings in blood pressure no longer appeared during the period of apnea (Fig. 2B), even though ventilation was arrested for longer periods of time than during the control period and the average arterial $P_{CO_2}$ at the end of the apnea was 134 mm Hg rather than 81 mm Hg. The abolition of the waves by alpha-adrenergic blockade, despite the extraordinarily intense chemical stimulus, indicates that the waves were vasomotor in origin.

Denervation. In the other 6 dogs (Table 1), ventilation was arrested before and after denervation of the peripheral chem- and baroreceptors. In each dog, the swings in blood pressure persisted although they decreased in amplitude and had a somewhat longer period (Fig. 2C). However, the relationship between phrenic nervous activity and the swings in blood pressure remained as before; i.e., each swing in blood pressure was associated with one burst of phrenic nervous activity which occurred at the

**RESULTS**

**Arrested Ventilation**

In each of the 15 nonhemorrhaged dogs, regular swings in blood pressure occurred (both control groups labeled before in Table 1) during arrested ventilation. The arterial $P_{CO_2}$ ranged from 55 to 105 mm Hg; the arterial $P_{O_2}$ always exceeded 90 mm Hg; and the pH was regularly low and of the order of 7.1. The swings in the amplitude of diastolic pressure from the peak to the trough of the wave averaged 18 mm Hg and ranged between 5 and 40 mm Hg.

The period of the oscillations, measured as the interval between the peaks of two consecutive waves in pressure, ranged between 4 and 16 sec. In each dog, the period of the swing in blood pressure was the same as the interval between the bursts of respiratory activity as signaled by discharges from the phrenic nerve (Fig. 2D). Therefore, the blood pressure waves in these nonhemorrhaged animals corresponded to the usual description of Traube-Hering waves.
Artificial Ventilation and Hemorrhage

In order to determine the effect of respiratory pattern, i.e., the integrated electrical activity and the frequency of the phrenic nerve bursts on the swings in blood pressure in hemorrhaged animals, nerve discharges were recorded from the phrenic nerve in 30 dogs which were hemorrhaged gradually until swings in blood pressure occurred. These swings in diastolic pressure varied between 5 and 50 mm Hg and were associated with four different patterns of phrenic nerve discharge. These are shown in Figs. 3 and 4. In none of these four patterns was the rate at which bursts of phrenic nerve activity occurred the same as the rate of the artificial ventilation.

In Fig. 3A, both the frequency of the bursts and the integrated electrical activity of the successive bursts are regular. The interval between the two peaks of the waves in systemic blood pressure is greater than the interval between the bursts of activity in the phrenic nerve, and there is no clear relationship between the respiratory pattern and the swings in blood pressure. Therefore, these blood pressure oscillations are categorized as Mayer waves.

The pattern of the swings in blood pressure, shown in Fig. 3B, is also regular, both in amplitude and in frequency; but, in contrast to Fig. 3A, the blood pressure swings with each burst of activity in the phrenic nerve, and there is one burst of nervous activity for each swing in blood pressure. These swings correspond to Traube-Hering waves. Although most Traube-Hering waves seen in hemorrhaged animals had a shorter period than did Mayer waves, the period of the Traube-Hering wave in Fig. 3B is the same as the Mayer wave in Fig. 3A. It is, therefore, apparent from Fig. 3, A and B, that in artificially ventilated animals it is difficult to use the period of the blood pressure swing to distinguish a Traube-Hering wave from a Mayer wave.

Like the Mayer waves, the period of the swings in blood pressure shown in Fig. 4, A and B, exceeds the interval between breaths. However, as in the Traube-Hering waves, there appears to be some relationship between the swings in blood pressure and respiratory activity as reflected in the bursts of phrenic activity. Thus, in Fig. 4A, there are two bursts of phrenic nerve discharge for each swing in blood pressure. The bursts are somewhat irregular and differ in size. The larger of the paired bursts occurs at the time of the increase in pressure to peak levels; the smaller burst of the two is associated with less change in blood pressure. In Fig. 4B, the waves in blood pressure have a smoother appearance and the phrenic nerve discharges are fairly constant in size. But, the frequency of phrenic nerve bursts is irregular. Thus, a rapid succession of bursts, in clusters of three or four, is associated with an increase in blood pressure to its summit. Waves of the type shown in Fig. 4, A and B, are difficult to classify either as Traube-Hering or Mayer waves, and will be called indeterminate waves in this report.

Adrenergic blockade. Phenoxybenzamine was given to seven hemorrhaged dogs with Mayer waves (Table 2). In each of the dogs, the waves disappeared after alpha-adrenergic blockade (see METHODS). The abolition of the waves by the phenoxybenzamine indicates that the swings in blood pressure which occurred in the hemorrhaged animals, like those described above (Table 1) for arrested ventilation, were vasomotor in origin.

Denervation. It was shown above (Table 1) that the Traube-Hering waves, which occurred during arrested ventilation in nonhemorrhaged animals, persisted after denervation of both carotid and aortic chemosensitive receptors. In a separate series of dogs, the denervation experiments were repeated in dogs with Mayer waves. The Mayer waves were produced by graded hemorrhage in six anesthetized dogs which had been paralyzed using succinylcholine and were artificially ventilated. Prior to the hemorrhage, their carotid sinus nerves were exposed bilaterally but left intact. After control records, the nerves were divided bilaterally. As may be seen in Table 3, denervation of the
TABLE 2. Effect of phenoxybenzamine on Mayer waves in seven hemorrhaged dogs

<table>
<thead>
<tr>
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<th>After</th>
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<tr>
<td>Systemic blood pressure, mm Hg</td>
<td>127/57 ±23/16</td>
<td>84/45 ±21/18</td>
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<tr>
<td>Amplitude of blood pressure waves, * mm Hg</td>
<td>12±4</td>
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<td>Interval between peaks of blood pressure waves, sec</td>
<td>18±4</td>
<td>0</td>
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<td>Amplitude of phrenic nerve integration, arbitrary units</td>
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<td>Interval between phrenic nerve bursts, sec</td>
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<tr>
<td>Arterial Pco2, mm Hg</td>
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<td>Arterial PsO2, mm Hg</td>
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</tr>
<tr>
<td>Arterial pH</td>
<td>7.19±.18</td>
<td>7.09±.17</td>
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Values are means ±1 sd. * Variation in diastolic pressure.

carotid chemo- and baroreceptors does not abolish the waves; they persist but are diminished in amplitude. Preservation of the Mayer waves after carotid chemo- and baroreceptor denervation is shown in Fig. 5, indicating that the carotid receptors are not necessary for Mayer waves to occur.

In two of the six dogs in which Mayer waves had persisted after cutting the carotid sinus nerves, the vagi were subsequently cut. In these two dogs, the bilateral vagotomy converted the Mayer waves to Traube-Hering waves. The effects of vagotomy, per se, on Mayer waves was investigated as part of the experiments, to be described in the next section.

Comparison of Traube-Hering and Mayer waves and their interconversion. In the 30 hemorrhaged dogs, Traube-Hering waves occurred on 58 occasions; Mayer waves occurred on 51 occasions. In these 30 dogs, the average systemic blood pressure during Traube-Hering waves was 104/76 mm Hg; this value was not significantly different (P > .05) from the average blood pressure of 108/57 mm Hg during Mayer waves. However, the integrated activity of individual phrenic nerve bursts was 59% more, and the frequency of the phrenic nerve bursts was 50% less during Traube-Hering waves than during Mayer waves. Both differences, i.e., in the frequency of the bursts of activity and in the integrated electrical activity, were statistically significant (P < .05).

In 12 of the 30 dogs, only Traube-Hering waves occurred during the graded hemorrhage, while in the other 18 hemorrhaged dogs, both Traube-Hering and Mayer waves occurred at different times. The characteristic features of the Traube-Hering and Mayer waves in the 18 dogs in which both wave forms occurred are summarized in Table 4. As shown in Table 4, the systolic blood pressure during Mayer waves averaged 27 mm Hg less and diastolic pressure 15 mm Hg less than during Traube-Hering waves. Also, the bursts of phrenic nervous activity occurred twice as frequently during Mayer waves, and the integrated activity of each nerve burst during Mayer waves was only 40% of the integrated activity measured during Traube-Hering waves. Each of these differences between Traube-Hering and Mayer waves was statistically significant (P < .01). On the other hand, the difference in blood gas tensions and pH shown in Table 4 was not significant (P > .05).

The fact that 12 dogs developed only Traube-Hering waves despite severe hemorrhagic hypotension (BP = 50 mm Hg) indicates that hypotension, per se, was not responsible for converting Traube-Hering to Mayer waves. Also, in the 18 dogs which showed both Mayer and Traube-Hering waves during the graded hemorrhage, either wave...
TABLE 4. Comparison of Traube-Hering and Mayer waves in 18 hemorrhaged dogs

<table>
<thead>
<tr>
<th></th>
<th>Traube-Hering</th>
<th>Mayer</th>
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<tbody>
<tr>
<td>Systemic blood pressure, mm Hg</td>
<td>159/93 ±26/29</td>
<td>132/76 ±23/14</td>
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<tr>
<td>Amplitude of blood pressure waves,* mm Hg</td>
<td>9±4 17±12</td>
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</tr>
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<td>Interval between peaks of blood pressure waves, sec</td>
<td>5±4 16±5</td>
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</tr>
<tr>
<td>Interval between phrenic nerve bursts, sec</td>
<td>64±62 31±34</td>
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<tr>
<td>Amplitude of phrenic nerve integration, arbitrary units</td>
<td>9±4 4±1</td>
<td></td>
</tr>
<tr>
<td>Arterial PCO₂, mm Hg</td>
<td>50±14 47±16</td>
<td></td>
</tr>
<tr>
<td>Arterial PO₂, mm Hg</td>
<td>71±29 74±22</td>
<td></td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.20±.15 7.21±.16</td>
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Values are means ±1 sd. * Variation in diastolic pressure.

could be present at any given level of systemic hypotension. On the other hand, Traube-Hering waves were regularly associated with larger (greater integrated electrical activity) and slower bursts of phrenic activity than were the Mayer waves, suggesting that Mayer waves might be converted to Traube-Hering waves, even at the same level of systemic blood pressure, if the frequency of the phrenic bursts were slowed or if the amplitude of the bursts were increased, or both.

Therefore, in 15 dogs with Mayer waves produced by hemorrhage, the frequency of the phrenic nerve bursts was decreased and the size of each phrenic nerve burst was increased either by vagotomy or by arresting artificial ventilation. In order to hold blood pressure unchanged in these 15 dogs, each dog was bled as needed. In 6 of the dogs which had persistent Mayer waves, artificial ventilation was stopped. After the arrest of artificial ventilation, the phrenic nerve bursts decreased in frequency, and the integrated activity of each burst increased (as arterial PCO₂ increased and PO₂ decreased); the Mayer waves were converted gradually to Traube-Hering waves (Fig. 6). This figure shows that despite a virtually unchanged blood pressure, a change in phrenic nerve—and presumably respiratory center—activity can decrease the period of the waves in blood pressure and change a Mayer wave to a Traube-Hering wave.

In nine dogs, after bilateral vagotomy (while arterial blood pressure was held at the prevagotomy level by bleeding) (Table 5), the bursts of phrenic nerve activity also decreased in frequency and the amplitude of each burst increased. Mayer waves were again transformed to Traube-Hering waves (Fig. 7).

In the attempt to change a Traube-Hering wave to a Mayer wave by changing the pattern of phrenic nerve activity without changing the level of systemic blood pressure, anesthetized dogs, in which Traube-Hering waves had been produced by vagotomy, were heated by means of high-resistance electrical tapes which were wrapped around the body. In four of the dogs, an increase in rectal temperature to 39°C was associated with a precipitous drop in blood pressure and cardiac irregularities which could not be prevented by the infusion of blood, saline, and dextran. However, in two dogs in which systemic blood pressure was sus-

![FIG. 6. Conversion of Mayer waves to Traube-Hering waves by arresting ventilation in an animal with intact peripheral chemoreceptors.](http://ajplegacy.physiology.org/)

TABLE 5. Conversion of Mayer to Traube-Hering waves by bilateral vagotomy and by arresting ventilation

<table>
<thead>
<tr>
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<th>After</th>
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<td>Amplitude of blood pressure waves,* mm Hg</td>
<td>16±4 14±8</td>
<td>19±7 10±5</td>
</tr>
<tr>
<td>Interval between peaks of blood pressure waves, sec</td>
<td>18±2 8±3.0</td>
<td>19±3 5±1.3</td>
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<tr>
<td>Amplitude of phrenic nerve integration, arbitrary units</td>
<td>34±10 121±63</td>
<td>32±18 63±24</td>
</tr>
<tr>
<td>Interval between phrenic nerve bursts, sec</td>
<td>3.5±1.0 8±3.0</td>
<td>4±1.0 5±1.3</td>
</tr>
<tr>
<td>Arterial PCO₂, mm Hg</td>
<td>44±8 42±5</td>
<td>39±7 37±9</td>
</tr>
<tr>
<td>Arterial PO₂, mm Hg</td>
<td>75±9 66±8</td>
<td>97±9 79±9</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.24±.14 7.27±.15</td>
<td>7.24±.13 7.10±.18</td>
</tr>
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Values are means ±1 sd. * Variation in diastolic pressure.
RESPIRATORY DRIVE AND VASOMOTOR WAVES

FIG. 7. Conversion of Mayer waves to Traube-Hering waves by vagotomy. A: Mayer waves before vagotomy; B: Traube-Hering waves after vagotomy. Following vagotomy integrated activity of each phrenic nerve burst increased and one blood pressure swing occurred with phrenic nerve burst.

FIG. 8. Conversion of Traube-Hering waves to Mayer waves by raising body temperature to 39 C. A: Traube-Hering waves in a vagotomized, artificially ventilated animal before heating; B: Mayer waves after heating. Note that in B phrenic nerve bursts occur more rapidly and integrated activity of each burst is less than in A.

DISCUSSION

In the present study, in order to determine the effect of nervous discharge from the respiratory center on blood pressure waves, we abolished voluntary respiration in dogs and measured the pattern of nervous discharge from the respiratory center using a phrenic neurogram.

With respect to respiratory activity, two distinct patterns of swings in blood pressure were observed: 1) Traube-Hering waves, which occurred at a frequency of 4–16/min and were synchronous with regular bursts of electrical activity in the phrenic nerve—this type of oscillation occurred regularly during arrested ventilation and frequently during hemorrhage; and 2) the Mayer wave, which occurred at a frequency of 3–6/min., and was slower in frequency than the interval between phrenic nerve bursts—these waves occurred only in hemorrhaged animals. In the hemorrhaged animals, the respiratory bursts associated with Mayer waves were more frequent and smaller in amplitude than those seen during Traube-Hering waves. When respiratory activity was irregular, indeterminate waves which had some of the features of both Traube-Hering and Mayer waves were observed.

Conversion of a Traube-Hering to a Mayer wave was usually associated with an increase in the frequency of phrenic nerve bursts. On the other hand, bilateral vagotomy, or arresting ventilation, converted Mayer waves to Traube-Hering waves regularly in association with a reduction in the frequency of phrenic activity and an increase in the amplitude of each burst. These observations suggest that the pattern of phasic discharge from the respiratory center may determine whether a Traube-Hering or Mayer wave will occur in a hemorrhaged animal. It is, therefore, relevant to consider the possible ways in which these two types of systemic blood pressure waves can be related to respiratory activity in animals with controlled ventilation.

Traube-Hering Waves

There is little question that the Traube-Hering waves are related, in some way, to activity of the respiratory center...
since 1) in the present study (as illustrated in Fig. 4A), the amplitude of systemic blood pressure rise was often unequivocally related to the amplitude of the respiratory discharge; and 2) in a previous study, it was shown that Traube-Hering waves disappeared as the bursts of respiratory activity were reduced in amplitude by the administration of an amine buffer (trihydroxymethylamine) (4). The present study also showed that the peripheral chemos- and baroreceptors are not necessary for this linkage of vasomotor and respiratory activity since the Traube-Hering waves persisted even after these receptors were denervated. By exclusion, two likely alternatives remain: either that central chemoreceptors transmit afferent impulses to both respiratory and vasomotor neurons or that direct connections exist between the respiratory and vasomotor neurons themselves. The present study did not settle this question. However, the disappearance of the waves after phenoxybenzamine did show that the efferent pathway for the production of these waves involves the alpha adrenergic receptors of the sympathetic nervous system. This conclusion is also supported by the demonstration by others that sympathetic nerves discharge phasically at the same frequency as respiratory neurons during Traube-Hering waves (1, 15, 20).

**Mayer Waves**

Two different mechanisms have been invoked to account for the occurrence of Mayer waves: one, based on results obtained from hemorrhaged cats during spontaneous breathing, attributes the Mayer waves to a waxing and waning of chemoreceptor discharge (2, 17); the other discounts the importance of any specific respiratory chemoreceptor and, instead, attributes the Mayer waves to an instability in the system controlling blood pressure (3, 8, 21–23).

Even though previous studies have demonstrated that swings in blood pressure can occur in hemorrhaged, artificially ventilated animals which have had their carotid chemoreceptors excised (3, 10, 22, 23), they did not prove that the carotid chemoreceptors are unnecessary for the occurrence of Mayer waves. This uncertainty remained because the earlier studies could not distinguish between Traube-Hering and Mayer waves since they did not record respiratory activity as phrenic nerve discharges. The present study, however, did prove that Mayer waves can occur even though the carotid chemoreceptors have been denervated, thus supporting the previous interpretations (3, 8, 10, 12, 20, 21). Additional evidence provided by the present study for this view was the regular phrenic nerve activity during Mayer waves; it is difficult to conceive of cyclic discharge of the carotid chemoreceptors as the cause of swings in blood pressure without simultaneously producing cyclic variations in the output of respiratory neurons.

In the dog, the aortic chemoreceptors do seem to exert an important influence on the level of systemic blood pressure (5). However, in the present study, the production of Mayer waves in two vagotomized dogs indicates that intact aortic chemoreceptors are unnecessary for the occurrence of Mayer waves. Also, the stimulation of the aortic bodies, which must have occurred during arrested ventilation, did not prevent transformation of Mayer to Traube-Hering waves. By exclusion, therefore, the Mayer waves observed in the artificially ventilated dogs seem to be attributable to unstable blood pressure control rather than to cyclic variations in the discharge of specific peripheral chemoreceptors.

Since blood pressure is controlled by a negative-feedback system, instability can occur either because of an increase in controller gain or because of long time delays in the system (22). Both mechanisms for instability may be involved in the present experiments. An apparent increase in the gain of the vasomotor controller, which may simply be a function of the nonlinear stimulus-response curves of chemos- (7, 14, 18) and baroreceptors (2, 21, 22, 27), has been demonstrated in hemorrhage (21) and in cerebral ischemia (22, 23). In addition, the relatively long time delays involved in the vasomotor control of blood pressure would also facilitate the occurrence of blood pressure waves.

The present study suggests that even when increased controller gain and time delays are present (22–24), Mayer waves need not occur if the amplitude of each burst of respiratory nervous activity is sufficiently great.

**A Model of Blood Pressure Control**

Figure 9 illustrates a system of ventilatory and circulatory control which can explain the origin of both the Traube-Hering and Mayer waves observed in the present study. It differs from the previous model which we presented by including the effects of respiratory neurons on circulatory activity (8). The system is designed to keep the tensions of CO₂ and of O₂ at some desired level in the peripheral and central chemoreceptors. In addition, the system operates to maintain systemic arterial blood pressure and intrapulmonary pressure within some desired limits; therefore, circulatory and lung stretch receptors are included.

For convenience, the central vasomotor and respiratory neurons are grouped in Fig. 9 into "centers" although the idea that these neurons exist in diffuse networks is just as compatible with the present findings. The essential feature of this system is that information about the arterial blood pressure and about the chemical state of the chemoreceptors is transmitted to both respiratory and vasomotor neurons.
Stimulation of the peripheral chemoreceptors by hypoxia and hypercapnia, for example, not only increases respiratory activity but also raises blood pressure and thereby augments blood flow to the chemoreceptors (2, 13). Thus, the "negative feedback" to these chemoreceptors consists of a decreased \( P_{CO_2} \) and an increased \( P_{O_2} \) in the arterial blood supply to these chemoreceptors as well as an increase in flow which further restores the chemoreceptor gas tensions towards normal (2, 8, 15, 17). The increase in blood pressure, in turn, also enhances baroreceptor inhibition of vasomotor activity.

The fact that respiratory-linked vasomotor waves (Traube-Hering waves) occur when there is slow synchronous discharge of many respiratory neurons, even after the peripheral chemo- and baroreceptors have been removed, suggests that there may be a direct connection between respiratory and vasomotor neurons (dotted line in Fig. 9); when discharges occur simultaneously through a sufficient number of these connections, Traube-Hering waves would occur.

Even in hemorrhaged animals in which Mayer waves occur to facilitate the slow phasic discharge of respiratory neurons may be sufficient to produce Traube-Hering waves instead. Thus, the results of the present study suggest that Mayer waves occur only when two conditions are fulfilled: 1) there is insufficient phasic respiratory activity to exert a noticeable effect on blood pressure (only a few respiratory neurons are discharging simultaneously and at a rapid rate); and 2) there is an increase in the output of any of the chemo- or baroreceptors to the vasomotor center, resulting in unstable vasomotor control.

Finally, the scheme of controller organization shown in Fig. 9 also allows vasomotor activity to affect respiratory activity, thus explaining the irregular respiratory center activity associated with the "indeterminate" waves in blood pressure. Thus, as illustrated in Fig. 4A, a respiratory discharge might increase blood pressure and flow to the respiratory "centers" and chemoreceptors sufficiently so that respiratory stimulation would be reduced and the phrenic nerve burst following the peak of the pressure would be diminished in amplitude. Or, as in Fig. 4B, the increase in flow associated with the blood pressure wave could transiently suppress the subsequent respiratory discharge. It is clear from these observations that any model of the regulation of ventilation or circulation, the purpose of which is to account fully for integrative mechanisms, must include provision for the interplay between respiratory and circulatory control mechanisms under different experimental conditions.

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RESPIRATORY DRIVE AND VASOMOTOR WAVES