THE INTERRELATIONS OF VAGAL AND ACCELERATOR EFFECTS ON THE CARDIAC RATE

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Several studies have been made concerning the effects on the heart rate (h. r.) of simultaneous stimulation of the vagi and the accelerators (see Tigerstedt, 1921, for references). The conclusions drawn from the majority of these studies are qualitative. The only quantitative statement which we know is that of Hunt (1897), that the result of simultaneous stimulation of the two sets of nerve fibers is very nearly the arithmetical mean of the results of the isolated stimulations. The problem is of interest not only because of the reciprocal elevation and depression of the continuous tonic discharge in the two nerve supplies during reflex changes of h. r., but also because of its bearing on the mode of action of the autonomic nerves and on the interrelations of excitation and inhibition.

For these reasons the present quantitative study was undertaken.

METHOD. Cats were used, under dial anesthesia, which insures a stable basal h. r. if the temperature of the animal is maintained constant. The h. r. was recorded by means of a Marey tambour applied to the thoracic wall. The left vagus was stimulated in the neck. For cardio-accelerator stimulation the electrodes were applied to the internal branch of the right stellate ganglion, after severance of all the other connections of the ganglion. The right vagus was previously sectioned aseptically in the neck and time (about 8 days) was allowed for degeneration, to eliminate a possible perturbing spread when the accelerator was stimulated.

Maximal electric waves at variable frequencies were employed as stimuli. Each nerve was activated by a separate circuit so that independent variations of the frequencies could be obtained. The two stimulating circuits were a "multivibrator," delivering rectangular waves lasting about 1.0, and a condenser set connected with a mechanical interruptor.

Artificial respiration was administered when the thorax was opened to operate on the stellate ganglia. The rectal temperature of the animals was maintained between 37 and 38°C. No precautions were taken to eliminate the adrenals, for dial abolishes any demonstrable reflex secretion of adrenaline (unpublished observations).

Stimulation of the vagus for 10 seconds and the accelerator for 20 seconds
causes practically maximal changes of heart rate, i.e., a steady state is reached (see fig. 5). The vagus, therefore, was usually stimulated for 20 seconds, the accelerator for 30 seconds, and the heart rate during the last 10 seconds was recorded as the maximal response for the frequency employed.

In some animals high frequencies (usually above 8 per second) of stimulation of the vagus alone made the rate so slow that the ventricle escaped and beat at its own rhythm. This led to a break in the corresponding curves. Such observations were discarded.

**RESULTS.** A. Effects of vagal stimulation with and without a simultaneous tonic accelerator discharge. Cats under dial anesthesia have a persistent tonic accelerator discharge, especially marked if the vagi and depressors are sectioned and the carotids ligated. In such preparations the falls of blood pressure elicited by peripheral stimulation of the left vagus evoke a minimal or no change in this discharge because the main, if not all, circulatory proprioceptors have been inactivated. Under these circumstances, therefore, tonic accelerator impulses and stimulated vagal impulses are acting simultaneously, and the differences in the responses before and after severance of the accelerator supply give information concerning the role of each set of nerves when acting together.

Figure 1 illustrates these different responses. The left vagus was stimu-
lated for 20 seconds at various frequencies. The number of beats occurring during the last 10 seconds of stimulation was counted. The difference between this number and the basal h. r. per 10 seconds is plotted against the corresponding frequency. The curve A. i. represents the slowings obtained with the accelerators intact, the curve A. s. the responses after severance of the accelerators.

From these curves it would appear as if vagal stimulation were more effective when an accelerator discharge is present than when absent. The same data plotted as actual h. r. obtained (cf. fig. 11) would, on the contrary, give rise to the impression that the results of vagal stimulation are greater in the denervated heart. In figure 2, however, the slowings represented in figure 1 are expressed as per cent of the existing basal h. r. A single curve fits satisfactorily all the observations made. Similar results were found in all the preparations tested. We may conclude that the percental slowing elicited by a given stimulation of the vagus is the same whether a simultaneous accelerator tonic discharge is present or not.

B. Simultaneous stimulation of the two sets of cardiac nerves at variable frequencies. In order to eliminate the possibility of variations in the accelerator tone while the vagus was activated and in order to ascertain whether the percental slowing evoked by a given stimulation of the vagus is independent of the degree of accelerator activity in all the physiologic range, the following experiments were performed. The heart was disconnected from the central nervous system. A series of responses to stimulation of the left vagus alone at various frequencies was recorded. Similar series were then obtained during the persistent stimulation of the right accelerator at a given frequency, different for each series (cf. fig. 11). It was found that the responses thus elicited again yielded a single curve when plotted as per cent of the corresponding pre-existing rates. Figure 3 illustrates two series of responses to vagal stimulation, the one, V, without and the other, V + A, with simultaneous persistent activation of the accelerator at a frequency of 8 per second. Figure 4 shows the similarity of effects when plotted as per cent of the basal. A similar agreement of percental effects was found with all degrees of activation tried (up to 20 per second, which is probably the maximum that the systems involved may attain: see Rosenblueth, 1932). A similar agreement was likewise found when the accelerator was stimulated for 30 seconds at various frequencies while the vagus was persistently activated throughout a series. This latter procedure was not applied extensively because of the technical disadvantage which ensues from the slower recovery after accelerator stimulation as compared with the rapid return to basal after vagal excitation (see fig. 5).

C. The time course of the responses to simultaneous stimulation of the vagus and the accelerators. The results reported in the two previous sec-
Cons show that the percental maximal effect of a given stimulus on one of the nerves is the same, no matter what degree of persistent simultaneous activation of the other nerve is applied. Are the percental effects at any given moment during simultaneous stimulation the same as those which would occur had one of the nerves been activated singly? The observations reported here furnish an answer to this question.

Figure 5 illustrates the time course of the responses to separate stimulation of the vagus, V, and of the accelerator, A, for 30 seconds, and to simultaneous excitation of the two nerves, V + A, with the same stimuli used for the separate activations. The slowing induced by the vagus alone is succeeded by a moderate acceleration, due probably to some accelerator fibers contained in the nerve (see Tigerstedt, loc. cit.). After simultaneous stimulation the slowing is promptly succeeded by marked acceleration, so that the h. r. rises to the values it would have had if the accelerator alone had been activated, and the two curves, A and V + A, thereafter almost coincide (cf. Baxt, 1875). A similarly close coincidence is observed on recovery from the slowing induced by stimulation of the vagus during the prolonged after-effects of previous excitation of the accelerator (fig. 6).
Figure 7 illustrates the effects of stimulating either the vagus, \( A + V \) or the accelerator, \( V + A \), while the other nerve was being continuously activated before (30 seconds or more) and throughout the observation. The frequencies employed on each nerve were the same as those applied for the responses recorded in figure 5. That the percental effects of each nerve on the rate imposed by the other are the same at any moment as would obtain if activated alone is shown in figure 8. The circles are the effects of the accelerator and vagus alone in figure 5, plotted as per cent of the basal rate of the denervated heart. The dots are the responses in figure 7, plotted as per cent of the rates elicited by the persistent stimulation of either nerve. The percental effects are seen to be practically the same throughout the observations.

DISCUSSION. The data presented (figs. 2, 4 and 8) show that a given stimulation of the decelerator nerves induces the same percental degree of slowing, independently of whether the accelerators are excited or not, other variables being kept constant (temperature, etc.); and vice versa, a given stimulation of the accelerators evokes a given percental increase of h. r. which is independent of decelerator excitation. Such being the case, the results of simultaneous stimulation of the two sets of nerves should in
general differ from the arithmetical mean of the separate effects. Figure 9 illustrates this difference. Curve V denotes the responses of a decentralized heart upon stimulation of the vagus alone at various frequencies. The accelerator was now persistently activated with a frequency of 8 per second, whereupon the h. r. went from 25 to 43.5 beats per 10 seconds. A series of responses to the vagus was then recorded, while stimulation of the accelerator was maintained. The broken line A. M. denotes the effects which would have been obtained if the responses to simultaneous activation were the arithmetical mean of the separate effects. The actual values found are plotted in curve A + V. Similar tests eliminated the concepts of algebraic summation or geometrical mean, the deviations being beyond the limits of experimental errors. Hunt (loc. cit.) obtained approximately the arithmetical mean. This was probably due to his working near the region of intersection of the curves a. m. and A + V in figure 9.

We infer that the effects of simultaneous stimulation of the decelerators and accelerators is the resultant of the two opposite influences. The two nerves act independently; neither interferes with the other; each exerts its action on the rate imposed by the other as if this were not active.

These results and inferences are consistent with the theory of chemical
mediation of autonomic nerve impulses. Several possibilities could be expected from this theory. For instance, either one of the mediating substances could inactivate the other, or the two could act independently on the pacemaker. The experimental data presented confirm the latter suggestion and invalidate the former. The possibility that the rhythm of the denervated heart could be a function of the persistent local metabolic production of sympathin and that vagal stimulation would inhibit this production is thus excluded.

Fig. 9. Ordinates: h. r. per 10 seconds. Abscissae: frequencies of stimulation applied to the vagus. \( V \) (circles): vagus alone. \( A + V \) (dots): vagus during persistent stimulation of the accelerator at 8 per second. The curve \( a. m. \) (crosses) denotes the effects which would have obtained in the latter case if the responses to simultaneous stimulation of the two nerves were the arithmetical mean of the responses to separate activation.

Fig. 10. Test of the curves in figure 12 as hyperbolas. Ordinates: \( F/R \). Abscissae: \( F \). \( V \) (dots): vagus. \( A \) (circles): accelerator. For explanation see text.

The post-acceleration on simultaneous excitation of the two nerves (fig. 5) is readily explained in terms of the rates of destruction of the two mediators; the vagal substance is rapidly destroyed, thus permitting the more stable sympathin to exert its influence. From the data reported in section C we may further conclude that the rates of production and destruction of each of the substances are not modified by the presence of the other mediator.

The post-acceleration has led to the inference that the "point of attack" (\textit{Angriffspunkt}) of the two nerves on the pacemaker is not the same (Tigerstedt, 1921; Asher, 1926). This inference appears to be unwarranted. The opposite effects are probably exerted on the same structure or process,
but one ceases before the other. The problem of the antagonism between the two nerves is intimately related to the preceding concept. Since the influences may be exerted on the same structure and the responses bear opposite signs, the effects would be strictly antagonistic.

The physiological consequences of the tonic presence of the two opposed influences and of their reciprocal decrease or intensification in reflex changes of h. r. in the higher vertebrates may be clarified by the following speculations. Changes of h. r. could be elicited in four ways: a, a single nerve supply slowing a fast heart; b, a single nerve supply accelerating a quiescent or slow heart; c, a dual supply, accelerating and decelerating, respectively, a heart with an average rhythm, and never acting simultaneously, but separately; d, finally the actual situation, a dual supply acting constantly, and reciprocally excited and inhibited. The situations a and b occur in some molluscs (see Tigerstedt, loc. cit., for references). An analysis of the curves in figure 12 leads to the inference that to obtain a given rate with a single nerve supply would require either a higher frequency of discharge or a larger quantum of mediator per nerve impulse (see Rosenblueth, 1932). A dual nerve supply permits, therefore, a finer gradation. In situation c recovery from a given slowing or, more specially, acceleration, would be long (cf. curves A and A + V, fig. 6). The consequences of the physiological situation d are then the possibility of obtaining considerable changes with relatively slow frequencies of nerve discharge, a fine gradation and the possibility of rapid changes.

The significance of the percental scale adopted to estimate the effects of a given stimulus (figs. 2, 4 and 8) instead of the absolute decrement or increment in heart beats per unit time (figs. 1, 3, 5, 6 and 7) will appear from the following considerations. Stimulation of the accelerators or the decelerators does not add to or subtract from the existing rate a certain number of beats; its multiplies the rate by a given factor greater or less than 1; in other words, the degree of acceleration or deceleration obtained is a function of the existing rate on which the stimulus acts. Suppose, adopting a classical view, that the h. r. depends on the length of the refractory period (absolute and relative) and that a given stimulation of the vagus increases this length by a certain amount, say 1 second. Suppose now that this stimulus is applied while the refractory period is 2 seconds. The basal rate of 30 beats per minute will be slowed to 20 during the stimulation; the actual deceleration will then be 10 beats. If the same excitation of the vagus, however, should be performed when the refractory period is 1 second, the rate would go from 60 to 30, an actual slowing of 30 beats per minute. Thus, even if the effects of the vagus should be additive on the refractory period the influence on diverse basal rates would not be additive, but multiplicative. A similar reasoning holds for any other theory adopted to explain the mode of action of the nerves on the h. r. Acceleration and
deceleration, then, not being additive, the concepts of an arithmetic mean or an algebraic summation are a priori excluded (see p. 47).

It is interesting to contrast the independence of effects of the excitatory and inhibitory influences in the heart with the dependence of an inhibitory effect on previous excitation in the central nervous system. In the moto-neurones, as shown by Sherrington (1925), c.i.s. acts on c.e.s., not on the neurone itself; thus inhibition can only be apparent if excitation is induced. In the heart, on the other hand, the opposed influences are exerted on the pacemaker itself, and vagal effects do not therefore require accelerator tone for demonstration. It is tempting, but premature, to speculate as to whether in neurones that apparently do not require afferent nerve impulses for activation, such as those in the respiratory center, c.e.s. and c.i.s. do not bear relations similar to those found in the heart for the accelerating and decelerating substances.

MATHEMATICAL DISCUSSION. The curves correlating the frequency of stimulation of accelerators or decelerators with the maximum of the corresponding responses at equilibrium, plotted as either absolute (figs. 1 and 3) or percental (figs. 2, 4 and 12) increments or decrements of the h. r. have been previously (Rosenblueth, 1932) shown to be rectangular hyperbolas of the form

\[ \pm \Delta R = \frac{F}{k + k'F} \]  

(1)

where \( \Delta R \) denotes the increment (+) or decrement (−); F, the frequency; and \( k \) and \( k' \), constants.

From (1)

\[ \frac{F}{\Delta R} = k + k'F. \]

A simple test of the adequacy of the formula to fit the experimental data is, therefore, to plot \( F/\Delta R \) against F; a straight line should obtain. An application of this test to the curves in figure 12 is shown in figure 10.

In order to deal with the effects of simultaneous stimulation of the two nerves, the following formulation is convenient. Let B denote the basal rate of the heart when not influenced by any nerve impulse; R and F, as in (1); and the suffixes a and v, accelerator and vagus, respectively. Then,

\[ R_a = mB = B \left[ 1 + \frac{F_a}{B(k + k'F_a)} \right] \]  

(2)

where \( m > 1 \). And

\[ R_v = nB = B \left[ 1 - \frac{F_v}{B(c + c'F_v)} \right] \]  

(3)

where \( n < 1 \).
If the effects of the two nerves coexist independently,
\[ R_{a+v} = mB \]..............(4)

If now \( F_a \) is constant, \( m = \alpha \) (constant), then
\[ R_{a+v} = \alpha B \left[ 1 - \frac{F_v}{R(c + c'F_v)} \right] \]..............(5)

And similarly, if \( n = \beta \) (constant), then
\[ R_{a+v} = \beta B \left[ 1 + \frac{F_a}{B(k + k'F_a)} \right] \]..............(6)

In (5),
\[ \alpha B - R_{a+v} = \frac{\alpha F_v}{c + c'F_v} = \Delta R_{a+v} \]

Hence,
\[ \frac{\alpha F_v}{\Delta R_{a+v}} = c + c'F_v \]

That is, the curves \( A.i. \) (fig. 1) and \( V + A \) (fig. 3) should again be rectangular hyperbolas, and \( F/\Delta R \) plotted against \( F \) should yield a straight line. This test was applied to all the experimental curves with satisfactory results.

The interrelations of the three variables \( R, F_a \) and \( F_v \) are best appreciated by means of nomograms. By use of the method described in section B an experimental family of curves may be obtained, such as is represented in figure 11. The procedure used involves a large number of determinations, whereupon a certain scattering ensues. The close similarity of this experimental family of curves with the theoretical contour nomogram in figure 13 is, however, striking. In order to construct the theoretical nomograms the values of \( k \) and \( k' \) and \( c \) and \( c' \) were calculated from the data in figure 12, obtained in the same animal on which the observations of figure 11 were made. Figure 13 illustrates the h. r. corresponding to variable degrees of stimulation of the vagus, the accelerator being activated with constant given frequencies. If this figure is slabbed by vertical lines and the \( F_a \) corresponding to the curves is plotted against the \( R \) at the intersection of the line and the curve, the family in figure 14 is obtained, which depicts the responses to variable stimulation of the accelerators with simultaneous activation of the vagi at a given frequency. Vertical slabbing of this figure yields back figure 13. Horizontal slabbing of either of these two families gives figure 15, which shows what frequencies on the two nerves will elicit a given h. r. Vertical slabbing of figure 15 leads back to figure 14, while horizontal slabbing restores figure 13. Angular slabbing through the origin of figure 15 yields figure 16, which represents the responses to various frequencies on the two nerves, the ratio of \( F_a / F_v \) being constant.
Fig. 11. Experimental family of curves obtained by means of the method described in section B. Ordinates: h. r. per 10 seconds. Abscissae: frequencies applied to the vagus. The indices of the curves denote the frequency of persistent activation of the accelerator.


Fig. 13. Theoretical contour chart. Ordinates: heart rate per 10 seconds. Abscissae: frequency of stimulation of the vagus. Indices of the curves: frequency of stimulation of the accelerator. The basal rate of the denervated heart in this and the succeeding figures is 24 per 10 seconds.

Fig. 14. Theoretical contour chart. Ordinates: heart rate per 10 seconds. Abscissae: frequency of stimulation of the accelerator. Indices of the curves: frequency of stimulation of the vagus.
If the data in figures 13 and 14 are plotted as percental acceleration and deceleration, respectively, figure 12 ensues. This figure shows that the curves of acceleration and deceleration are not continuous. There is a discontinuity at the origin. This is in keeping with the idea expressed above (p. 48), that we are dealing with two independent influences neither of which is similar to the factor responsible for the autonomous rhythm.

The contour nomograms in figures 13, 14, 15 and 16 are advantageous in permitting the selection of the dependent and independent variables. If, however, it is desired to examine the interrelations with new variables, e.g., $O_2$ consumption, heat production, etc., the pictures would become too complex for ready interpretation. Figure 17 is a scalar nomogram which summarizes the contour charts. If any two of the variables are selected, the third will be determined by a straight line through the two known values, as usual. The scales on the lines $F_a$ and $F_v$ are hyperbolic, that on H. R. is logarithmic. To this nomogram an indefinite number of scales may be added, representing new correlated variables, such as those mentioned above.

The preceding formulation covers only temporal variations of the stimuli applied to the nerves. Spatial variations can, however, be dealt with by means of the same nomograms. The scales marked $F$ can denote $N$ (number of nerve impulses per unit time), for $N = nF$, where $n$ is the number

![Fig. 15](image1)

**Fig. 15.** Theoretical contour chart. Axes: frequency of stimulation; ordinates, accelerator; abscissae, vagus. Indices of the curves: heart rate per 10 seconds.

![Fig. 16](image2)

**Fig. 16.** Theoretical contour chart. Ordinates: heart rate per 10 seconds. Abscissae: frequency of stimulation of the accelerator. Indices of curves: ratio $F_a/F_v$. For explanation see text.
of nerve fibers involved (see Rosenblueth and Rioch, 1933). In the experiments here reported \( n \) was kept constant by using maximal stimuli.

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Fig. 17. Scalar nomogram. \( P_a \): frequency of stimulation of the accelerator. H. R.: heart rate per 10 seconds. \( P_v \): frequency of stimulation of the vagus.

**SUMMARY**

The changes of heart rate at equilibrium on stimulation of the vagus at various frequencies, with and without a simultaneous constant accelerant tonic discharge (fig. 1), are similar for any frequency on the vagus when plotted as per cent of the corresponding basal rate (fig. 2).

The maximal percental effects of a given vagal stimulation are likewise the same (fig. 4) no matter what simultaneous activation of the accelerators is applied (figs. 3 and 11).

The independence of the percental effects on stimulation of either nerve from the simultaneous activation of the other exists not only at equilibrium, but throughout the time course of the responses (figs. 5, 6, 7 and 8; section C).
It is concluded that the effects of simultaneous excitation of the accelerators and decelerators is not the arithmetical mean (fig. 9), nor an algebraic summation, nor the geometrical mean of the responses to separate stimulation (p. 47), but the resultant of the two influences. The two effects occur independently, as if each set of nerves was acting alone.

This conclusion is discussed in relation to the following subjects: the chemical mediation of autonomic nerve impulses (p. 48), the “point of attack” of the two nerves on the pacemaker (p. 48), the implications of the tonic activity of the two nerves and the changes which occur in cardiac reflexes (p. 49), the multiplicative—not additive—nature of acceleration and deceleration (p. 49), and the interrelations of excitation and inhibition in the central nervous system (p. 50).

A mathematical discussion is presented (p. 50). This includes a graphic representation (figs. 13, 14, 15, 16 and 17) which correlates the variables involved.

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