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A mathematical model of heart rate control by sympathetic and vagus efferent information[1]

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THE EFFECT ON HEART RATE of stimulation of sympathetic and vagus efferent nerves to the heart has been described in a qualitative fashion by many investigators. However, except for the work of Rosenblueth and Simeone (1) in 1934, no attempt has been made to analyze in a quantitative way the dynamic relationship between heart rate and frequency of stimulation of these nerves. The present study was undertaken with the hope that such an analysis might yield useful information regarding *a*) the nature of the physical and chemical events involved in this transformation and *b*) the dynamic and steady state parameters of this link of the heart rate control system.

METHODS AND PROCEDURE

The experiments were performed on mongrel dogs anesthetized with pentobarbital (30 mg/kg). After the insertion of an endotracheal tube, the dog was maintained on positive pressure ventilation with 100% oxygen. Wide variation in the depth and rate of ventilation had no effect on the heart rate of such a dog once the sympathetic and vagus nerves had been severed.

An electrocardiogram was monitored on an oscilloscope throughout each experiment. If at any time the site of the pacemaker shifted from the sinoatrial (SA) node, as indicated by a change in the normal relationship between the P wave and the QRS complex, that segment of the record was not used in the analysis. Arterial pressure was recorded from the aortic arch by means of a plastic cannula introduced through the left carotid artery and connected to a pressure transducer. After amplification, the electrocardiographic and pressure-gauge signals were recorded on multichannel magnetic tape using frequency modulation at a tape speed of 1⅞ in/sec.

The stellate sympathetic ganglia were exposed through supraclavicular incisions without opening the chest. In some experiments, the postganglionic sympathetic nerves to the heart were isolated as they entered the vagosympathetic trunk inferior to the stellate sympathetic ganglia. In all experiments, the preganglionic nerve fibers entering these ganglia were identified as they passed posterior to the vertebral artery and were severed. The right and left vagus nerves were isolated and severed in the midneck region and the stimulating electrodes applied to the peripheral end of the cut nerves. By this means afferent stimulation was avoided, and the only efferent input arriving at the SA node was that due to the applied nerve stimuli. All sympathetic efferent nerves to the heart were not severed in these experiments; nevertheless, after the denervation described, no further variation in heart rate occurred even with extreme variations in arterial blood pressure. Depression of the central nervous system due to the anesthetic undoubtedly contributed to this absence of reflex variation in heart rate.

The nerve to be stimulated was placed across two platinum-iridium wires connected to the stimulator through an isolation transformer. Stimulus frequency was controlled as shown in Fig. 1. This illustrates the arrangement used to vary the frequency of stimulation in proportion to the amplitude of a sine, square, or triangular wave. The varying output voltage of a low frequency function generator was fed to an analogue computer, where it was biased and scaled. This, then, was the input of a voltage-to-frequency converter (Dymec model DY-2210, Dymec, Inc., Palo Alto, Calif.). To increase the accuracy of voltage-to-frequency conversion at low frequencies, the pulses from the frequency converter were fed to a counter, and the output of the second decade was used to trigger a stimulator. The output of the stimulator was a square wave of 1-msec duration and an amplitude greater than that required for maximal responses at any given stimulus frequency. (Usually this was 20 v.) The output voltage from the computer was recorded on tape as an analogue representation of the frequency of stimulation. In other experiments described elsewhere (2) information from the animal was fed to the computer and used to determine the frequency of stimulation.

Figure 2 shows the method used to derive heart rate from the recorded electrocardiogram. The recorded electrocardiogram from the tape reel is fed to the analogue computer where it is differentiated, and a certain amount of this derivative is added to the electrocardiogram using amplifier 1 in order to amplify the high frequency elements. This sum is then biased and rectified so that only positive spikes corresponding in time to each R wave appear at the output of the second amplifier. These spikes trigger a Tektronix saw-tooth generator, which in turn triggers two pulse generators in sequence. The pulses from these units each control a relay. A constant voltage is integrated by amplifier 3 to generate a saw tooth which is triggered back to its initial conditions by relay 2 at the onset of each heart cycle. Relay 1, however, closes first and allows amplifier 4 to reach the output voltage on amplifier 3. Relay 1 opens before amplifier 3 triggers back to its initial conditions and holds this final voltage until the next heart cycle is complete. The initial condition voltage on amplifier 3 is set at a positive value such that the time lost in relay closure will not prevent the voltage appearing on amplifier 4 from being exactly proportional to the period of the preceding heart cycle. Since heart rate is the reciprocal of the period, the output of amplifier 4 is divided into a constant generating a voltage proportional to the heart rate with each heart beat.

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This voltage is recorded on a tape loop along with the analogue voltage representing the frequency of sympathetic stimulation (f_1) and vagal stimulation (f_2).

Once the data have been recorded on a continuous loop of magnetic tape, the analysis is carried out as indicated in Fig. 3. The recorded heart rate is reproduced from the tape and displayed on one beam of a dual-beam oscilloscope. From another channel of the tape the analogue voltage representing f_1 or f_2, frequency of stimulation of sympathetic or vagus nerves, respectively, is fed to the computer. On the computer is programed the equations representing the theoretical relationship between frequency of stimulation and heart rate which is under test. The time course of heart rate predicted by this set of equations then is displayed on the other beam of the oscilloscope. The parameters of the equation may be varied by adjusting potentiometers in the computer. The parameters are varied systematically until an optimal fit between the predicted and recorded heart rate is obtained. To facilitate this analysis, the data from the tape loop was reproduced at tape speeds eight times the speed at which the data was initially recorded. Once the optimal set of parameters has been determined for step changes in f_1 or f_2, the ability of the equation to predict heart rate from sinusoidal, triangular, or square wave variations in sympathetic and parasympathetic stimulation frequency was tested. Permanent records of the predicted and experimental heart rates were obtained by use of an X-Y plotter or photokymographic recording assembly.

TABLE 1. *Representative values for equation constants*

$(k_1 n)\ (k_4)$	= .356
k_2	= 6.05/sec
k_3	= 0.25/sec
k_5	= 0.13/sec
k_7	= 2.75/sec
k_8	= 0.69/action potential
k_9	= 0.87/sec

Relationship of heart rate to f_1. In deriving a mathematical expression to describe the relationship between two variables such as heart rate, on the one hand, and frequency (f_1) of action potentials on the sympathetic efferent nerves to the

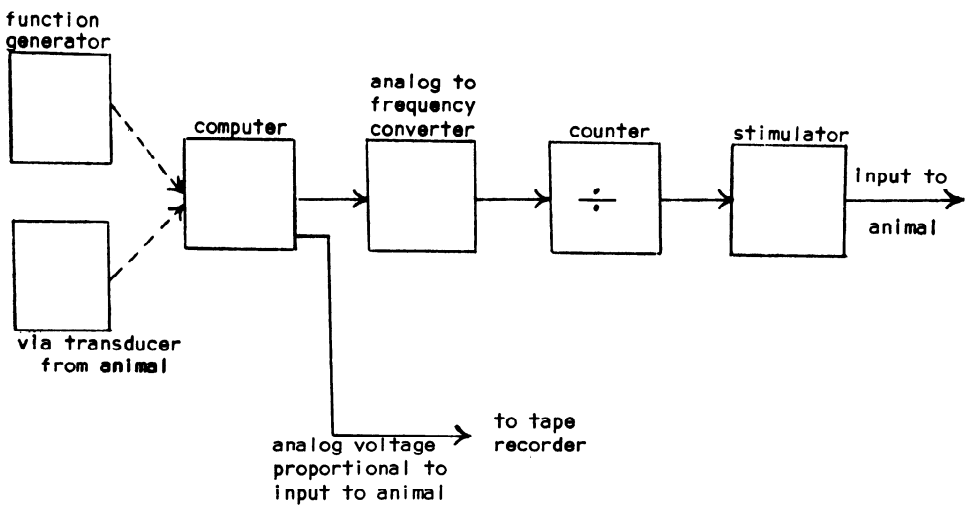


FIG. 1. Block diagram illustrating scheme used to derive stimulus frequency proportional to a varying analogue voltage.

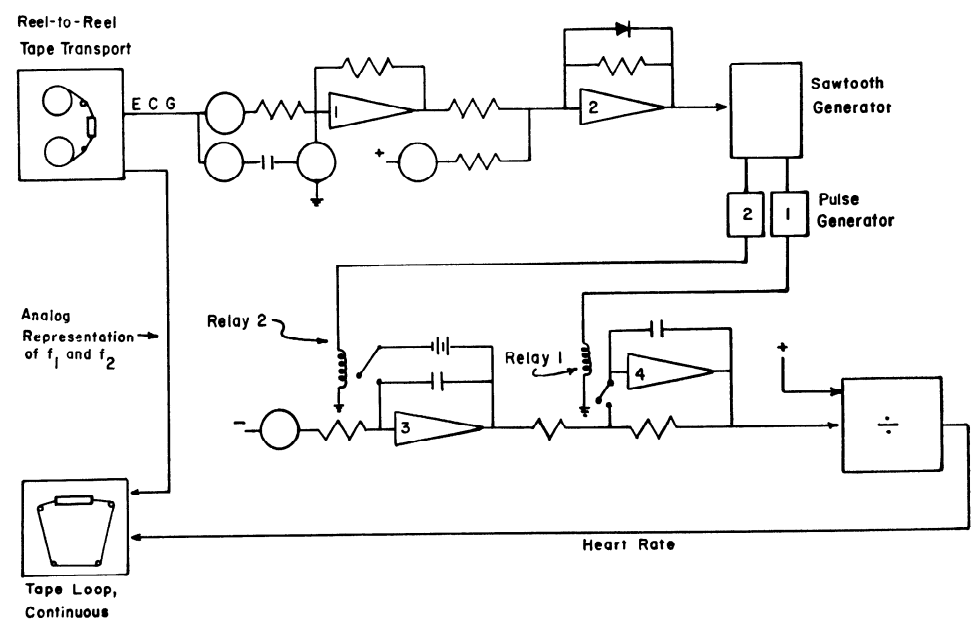


FIG. 2. Analogue computer program for deriving beat-by-beat measurements of heart rate from an electrocardiogram recorded on magnetic tape.

heart, on the other, the following procedure was used. First, recordings were made of the output response (heart rate) resulting from step increase and decrease in the input variable f_1. The heart rate response to two step inputs in f_1 of two different magnitudes is shown in Figs. 4 and 6. Several features of this response can be noted which must be accounted for by the theory. First, the heart rate response is asymmetrical, rising to its plateau value faster than it falls back to the control level after stimulation is stopped. Second, the rate of increase in heart rate following a sudden increase in frequency (f_1) of stimulation is dependent upon f_1; and, finally, it can be seen that the steady state response is nonlinear. The maximum change in heart rate resulting from stimulation at 2/sec is 50% of that resulting from stimulation at 20/sec.

The next step in formulating a hypothesis to describe such a system consists of drawing a block diagram to represent the physical and chemical processes thought to comprise this system. In doing this all available information concerning the system should be used in order that the final model found to describe the kinetic properties of the system may realistically account for the other properties known to be present. In Fig. 5 is shown a diagram representing our current concept of this system and the equations which describe its behavior. It is known that a chemical substance, norepinephrine, is released from sympathetic nerve endings when these nerves are stimulated (3). The lag in the response to stimulation is accounted for by the assumption that the released norepinephrine must diffuse to some active site in or on the cells of the SA node. Here a second-order chemical reaction is assumed to take place between the norepinephrine and some substance B in order to account for the observed nonlinearity of the system. *Equation 1* states that the rate of change of norepinephrine concentration (A_1) in the fluid surrounding the sympathetic nerve endings is equal to a constant (k_1) times the number of fibers (n) responding to each stimulus times the frequency of stimulation (f_1) plus a term which describes the equilibrium between blood concentration A_0 and A_1 plus a term representing the diffusion of norepinephrine to the active site on the SA node. Concentration at this site is labeled A_2. *Equation 2* describes the rate of change of concentration A_2 as equal to k_3 times the difference between A_1 and A_2 minus the rate at which A_2 is combining with B to form compound AB. *Equation 3* states that B is a substance present in constant amount whether it be free or combined with A. According to *equation 4* the production of compound AB is a second-order reaction proportional to the product of A_2 and B. The reaction rate constants in each direction are k_4 and k_5. *Equation 5* expresses heart rate as equal to the initial heart rate plus k_6 AB.

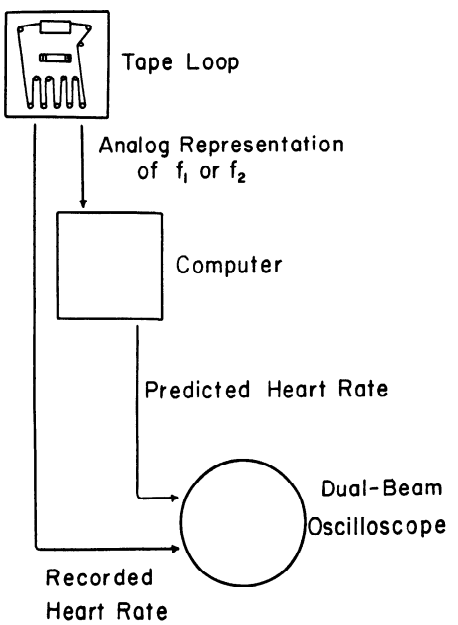


FIG. 3. Block diagram showing the arrangement used to test the ability of a mathematical model to predict the heart rate response to variations in frequency of sympathetic stimulation, f_1, or vagal stimulation, f_2.

It might be just as logical to assume that the second-order chemical reaction between A and B occurs elsewhere in this system; for instance, at the nerve ending prior to the release of norepinephrine. This would introduce the same type of nonlinearity into the response of the system. However, an experiment was performed which ruled out this possibility. The concentration of norepinephrine in blood (A_0) was raised to produce an increase in heart rate. Then f_1 was increased until the maximum heart rate was achieved. It was observed that the maximum heart rate achieved from sympathetic nerve stimulation was independent of the level of blood norepineph-

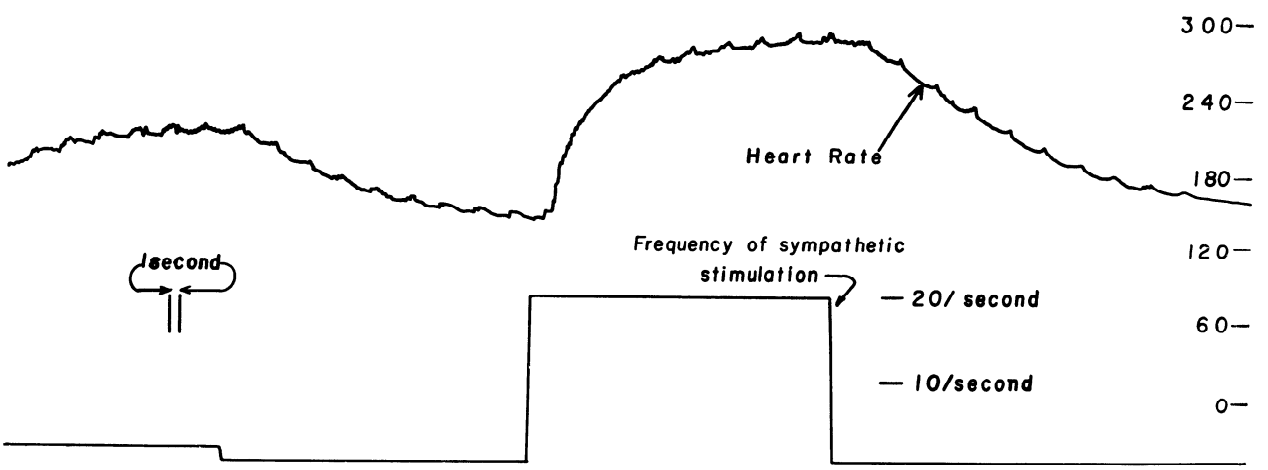
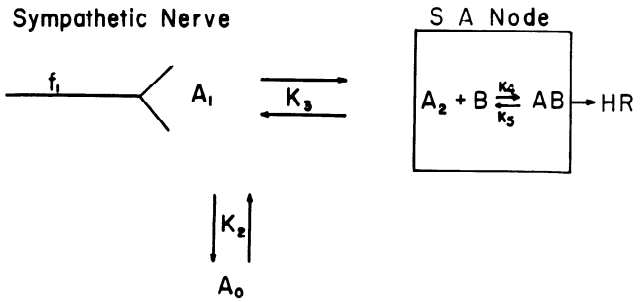


FIG. 4. Measured heart rate response to stimulation of preganglionic sympathetic nerves to the heart at frequencies of 2/sec and 20/sec.

rine concentration. Unless the elevated blood norepinephrine concentration affected the amount of norepinephrine released by sympathetic nerve stimulation, this observation supports the concept that the factor which limited the maximum heart rate obtainable was not in the amount of norepinephrine that could be released from the nerve ending but lay somewhere beyond this point as indicated by the mathematical model.

The constants for these equations may be uniquely determined by analysis of the response of two step inputs in f_1 of different magnitudes. Once these have been determined the ability of this mathematical expression to describe the time course of heart rate resulting from any pattern of the input f_1 may be predicted. Such a prediction for four step inputs is shown in Fig. 6. This model will also predict the time course of heart rate produced by sinusoidal and triangular wave variations in f_1. The accuracy with which these equations predict the time course of heart rate from a variety of input patterns makes it likely that the physical model proposed may actually represent the biological system. However, it cannot be concluded from the kinetic information alone that the intermediary steps proposed in this hypothesis are necessarily those existing in the animal. Some other scheme might exist which has the same general form as these equations and thus would just as well describe the observations. This model does predict, however, certain phenomena which can be checked with available techniques. A good example is the one referred to above; namely, the prediction that raising the concentration of norepinephrine in circulating blood would not affect the maximum heart rate achievable by sympathetic stimulation.



$$\frac{dA_1}{dt} = \frac{K_1 n f_1 + k_2(A_0 - A_1) + K_3(A_2 - A_1)}{V_1} \qquad \text{Equ. 1}$$

$$\frac{dA_2}{dt} = \frac{K_3(A_1 - A_2) - dAB/dt}{V_2} \qquad \text{Equ. 2}$$

$$B + AB = \text{constant} \qquad \text{Equ. 3}$$

$$\frac{dAB}{dt} = K_4(A_2)(B) - K_5 AB \qquad \text{Equ. 4}$$

$$HR = HR_0 + K_6 AB \qquad \text{Equ. 5}$$

FIG. 5. Block diagram and equations representing the relationship between frequency (f_1) of stimulation of sympathetic nerves to the heart and heart rate (HR). A_1 is the concentration of norepinephrine at the nerve ending, A_0 the concentration in blood, A_2 the concentration at the active site on the SA node; k_1, k_2, k_3, k_4, k_5, and k_6 are constants; B is a substance which must react with norepinephrine in order for the norepinephrine to produce a change in heart rate; n is the number of fibers responding to each stimulus, and HR_0 is the heart rate before stimulation; V_1 and V_2 are the apparent volumes into which A_1 and A_2, respectively, are diluted.

Heart rate versus f_2. Using the same methods, a mathematical expression for the dynamic relationship between heart rate and the rate of stimulation of the vagus nerve, f_2, may be derived. In Fig. 7 is shown the heart rate response to a step input in f_2. In this system also there is asymmetry between the on response and the off response, the on response occurring much more rapidly than the off. In fact, the minimum heart rate is often obtained within one heart beat after the onset of stimulation. The steady state relationship between heart rate and frequency of vagal stimulation is shown in Fig. 10.

The block diagram and equations used to represent the relationship of heart rate to the frequency (f_2) of vagal stimulation is shown in Fig. 8. At the end of each nerve fiber are many small vesicles which contain acetylcholine in concentration C_1. That such vesicles exist at some nerve endings has been demonstrated by electron microscopy (4). A fraction (k_8) of these vesicles discharge acetylcholine with the arrival of each action potential. The rate at which the number (N) of these vesicles (which are "charged" with acetylcholine and capable of discharging) changes with respect to time is shown in *equation 1*. N_m is a constant and represents the maximum number of charged vesicles achieved in a steady state when the nerve is not firing. With each action potential $k_8 N$ vesicles are discharged from each nerve ending decreasing the number of charged vesicles. The rate at which the number of charged vesicles is replenished is proportional to the difference between N and N_m; that is, at a rate proportional to the amount by

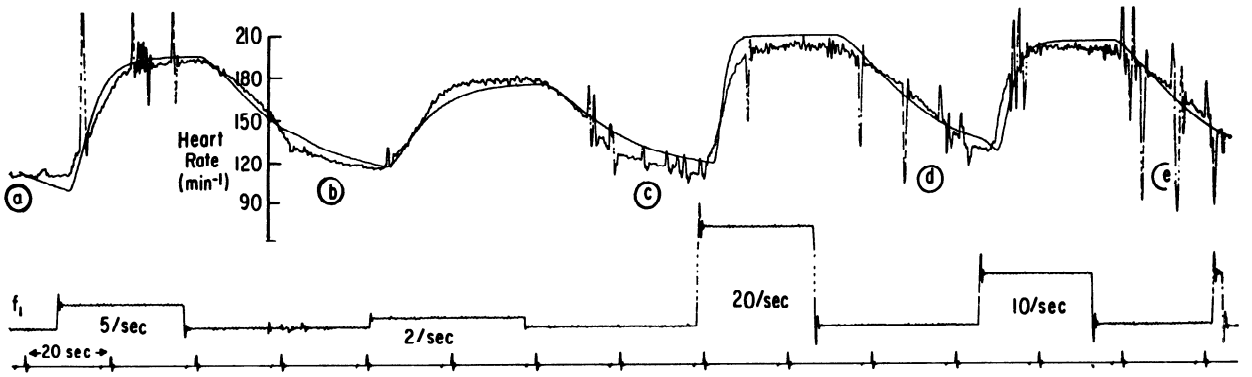


FIG. 6. Comparison of the observed and predicted heart rate response to four step inputs in the frequency (f_1) of sympathetic nerve stimulation.

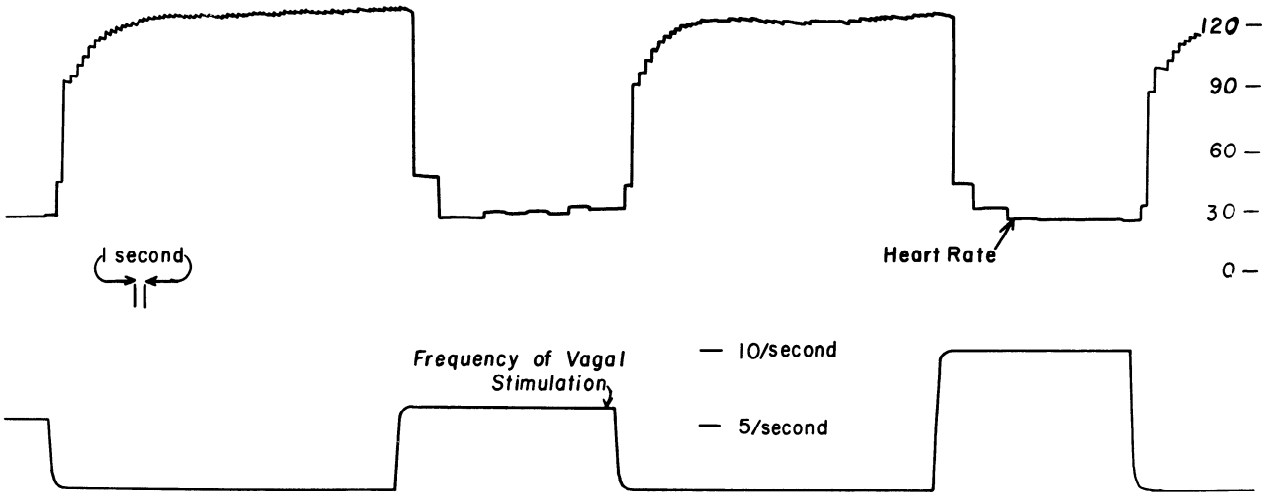
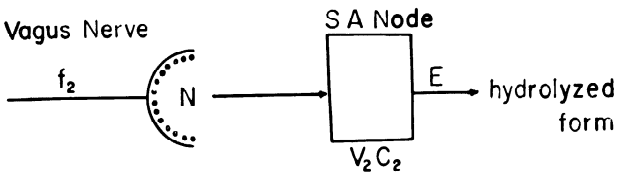


FIG. 7. Heart rate response to step increase and decrease in frequency (f_2) of stimulation of right vagus nerve.

which N is decreased from its resting value due to preceding action potentials. Although the experimental evidence is not yet sufficient to define the exact nature of the physical processes involved, the model does account for the nonlinear behavior of this system observed in the present experiments and is consistant with what knowledge is available at the present time regarding this system. C_2 is the concentration of acetylcholine at the SA node just outside the vesicle near the nerve ending. As shown in *equation 2*, this concentration will change at a rate which depends on f_2, on the product k_8C_1N, which is the amount of acetylcholine released by each action potential, and on n, the number of fibers responding to each stimulus. The



$$\frac{dN}{dt} = K_7(N_m - N) - K_8Nf_2 \qquad \text{Equ. 1}$$

$$\frac{dC_2}{dt} = \frac{nK_8NC_1f_2 - K_9C_2}{V_2} \qquad \text{Equ. 2}$$

$$P = P_0 + K_{10}C_2 \quad \text{for } C_2 < a$$

$$P = \infty \quad \text{for } C_2 > a \qquad \text{Equ. 3}$$

FIG. 8. Block diagram and equations representing the theoretical relationship between frequency (f_2) of vagal stimulation and period (P) of the heart cycle. N is the average number of vesicles at each nerve ending charged with acetylcholine; N_m is the maximum number of charged vesicles; k_7, k_8, k_9, k_{10}, and a are constants; C_1 is the concentration of acetylcholine in the vesicles, and C_2 the concentration in the fluid outside the vesicles at the SA node; V_2 is the volume into which this acetylcholine is diluted, and n is the number of fibers responding to the stimulus; P is the period of the heart cycle, and P_0 is the period of the heart cycle before vagal stimulation.

acetylcholine is hydrolyzed by the enzyme cholinesterase at a rate proportional to C_2. The rate of this reaction may be limited by the rate at which acetylcholine diffuses to a point of contact with cholinesterase. The values obtained for k_9 suggest this possibility (Table 1). V_2 is the volume into which the ejected acetylcholine is diluted. According to *equation 3*, the period (P) of the heart cycle will be changed by an amount proportional to C_2 as long as C_2 does not exceed some critical value (a).

The dynamic and steady state characteristics of this system can be described by these equations. In Fig. 9 is shown the time course of heart rate recorded after a step change in f_2 compared with the predicted heart rate using this mathematical model. The discrepancy between measured and predicted heart rate seen at the time heart rate is suddenly decreased is due to the fact that the method by which heart rate is measured introduces a lag equal to the time of the preceding heart cycle. The points plotted in Fig. 10 as crosses represent the period (P) of the heart cycle obtained for various frequencies (f_2) of vagal stimulation measured after the heart rate has become constant for a given rate of stimulation. The curve represents the period predicted by the steady state solution of the equations just shown. Note that the observed period follows closely the period predicted by the equation up to a critical point. At this point, further increase in f_2 results in sudden cardiac arrest with the period approaching infinity. This is thought to be the result of the pacemaker membrane potential's exceeding some critical value beyond which spontaneous depolarization cannot occur. This usually occurs when the period of the heart cycle exceeds 2 sec.

Heart rate versus f_1 and f_2. Now let us consider the relationship of heart rate to the frequency of stimulation of sympathetic (f_1) and vagus nerves (f_2) simultaneously. It was noted by Rosenblueth that the time constants for the heart rate response to f_1 and f_2 are not altered when one nerve is stimulated in the presence of a constant frequency of stimulation of the other (Fig. 11). Notice that the rate of decrease of heart rate with the onset of f_2 is still rapid, even in the presence of f_1, and that the slow rate of fall of heart rate after discontinuing f_1 persists even in the presence of f_2. These observations confirm those of Rosenblueth and are interpreted to indicate that the competitive effect of simultaneous stimulation must occur at some level in the system other than at those sites where variation in system parameters would alter the system kinetics.

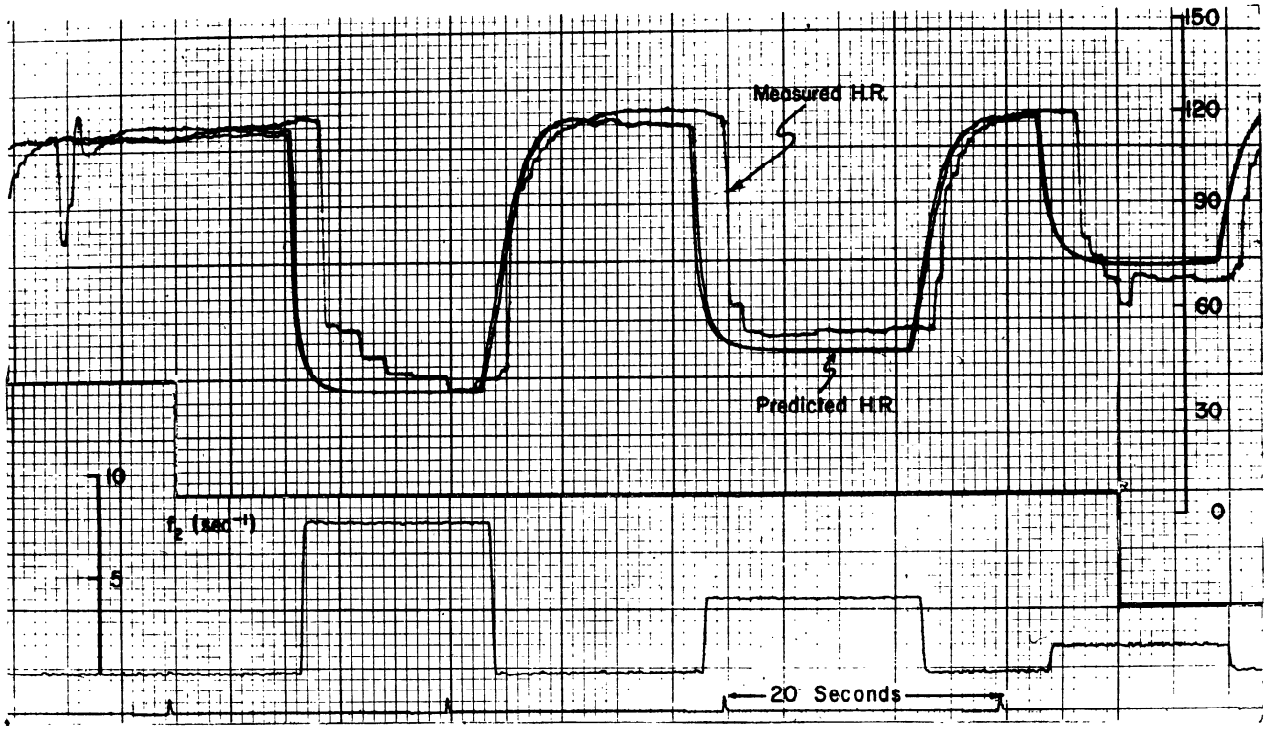


FIG. 9. Comparison of the observed and predicted heart rate (HR) response to vagal nerve stimulation (f_2).

Rosenblueth maintained that the response to f_1 in the presence of f_2 may be predicted if the responses to f_1 and f_2 alone are known. He stated that the heart rate response to f_1 will be proportional to the heart rate at the time stimulation of f_1 is begun. This relationship rarely holds in our experience. The most striking feature is the variability in the magnitude of the response to f_1 in the presence of f_2. In Fig. 11, for instance, it can be seen that the decrease in heart rate when f_1 is discontinued in the presence of f_2 (shown in the top recording) is much less than the rise in heart rate due to f_1 when vagus nerve stimulation (f_2) is begun first (as in the bottom recording). It is not uncommon in the presence of high frequencies of vagal stimulation to see no response whatever to sympathetic stimulation as long as the vagal stimulation is maintained. The relationship proposed by Rosenblueth does not hold under the conditions of our study. Further investigation into the nature of the pacemaker itself will be required before an adequate description of the combined effects of vagus and sympathetic nerves on heart rate will be possible.

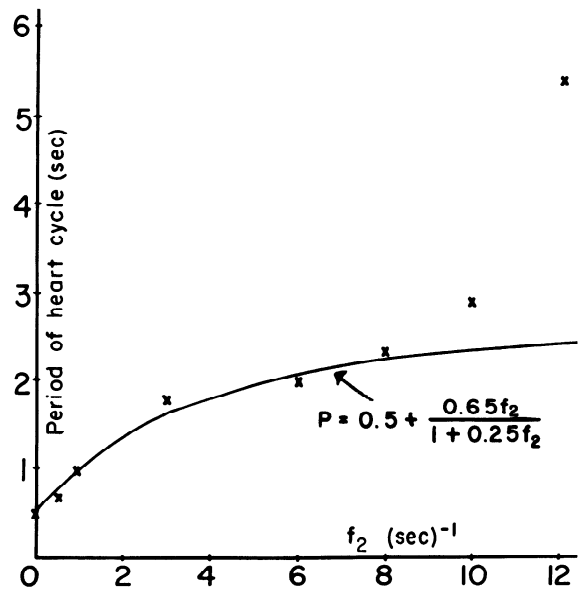


FIG. 10. Comparison of the observed period of the heart cycle measured after heart rate had become constant for a given frequency of stimulation (f_2) and the period predicted by the steady state solution of the mathematical model shown in Fig. 8.

DISCUSSION

The building of a mathematical model to represent systems such as those described in this paper may serve two useful purposes. First, the model represents an explicit, quantitative expression capable of describing all the observed characteristics of the system. In doing this the model brings into focus the cause-and-effect relationship between the parameters of the system and the dynamic characteristics of the system response to known input patterns. From a systematic investigation of the effect of varying each system parameter on system performance (easily accomplished with the help of a computer), new relationships and implications may become evident which may then be subjected to further experimental test.

The second and equally important advantage derived from "model building" of this type is the kinetic information itself. This information in the form of time constants and nonlinearities must be obtained in order that the role of this system as part of the over-all control mechanism for the circulation may be understood. To describe the control of the circulation as an integrated system, it is first necessary that this type of analysis be carried out for each reflex arch and hydraulic component of the whole circulatory system. The particular

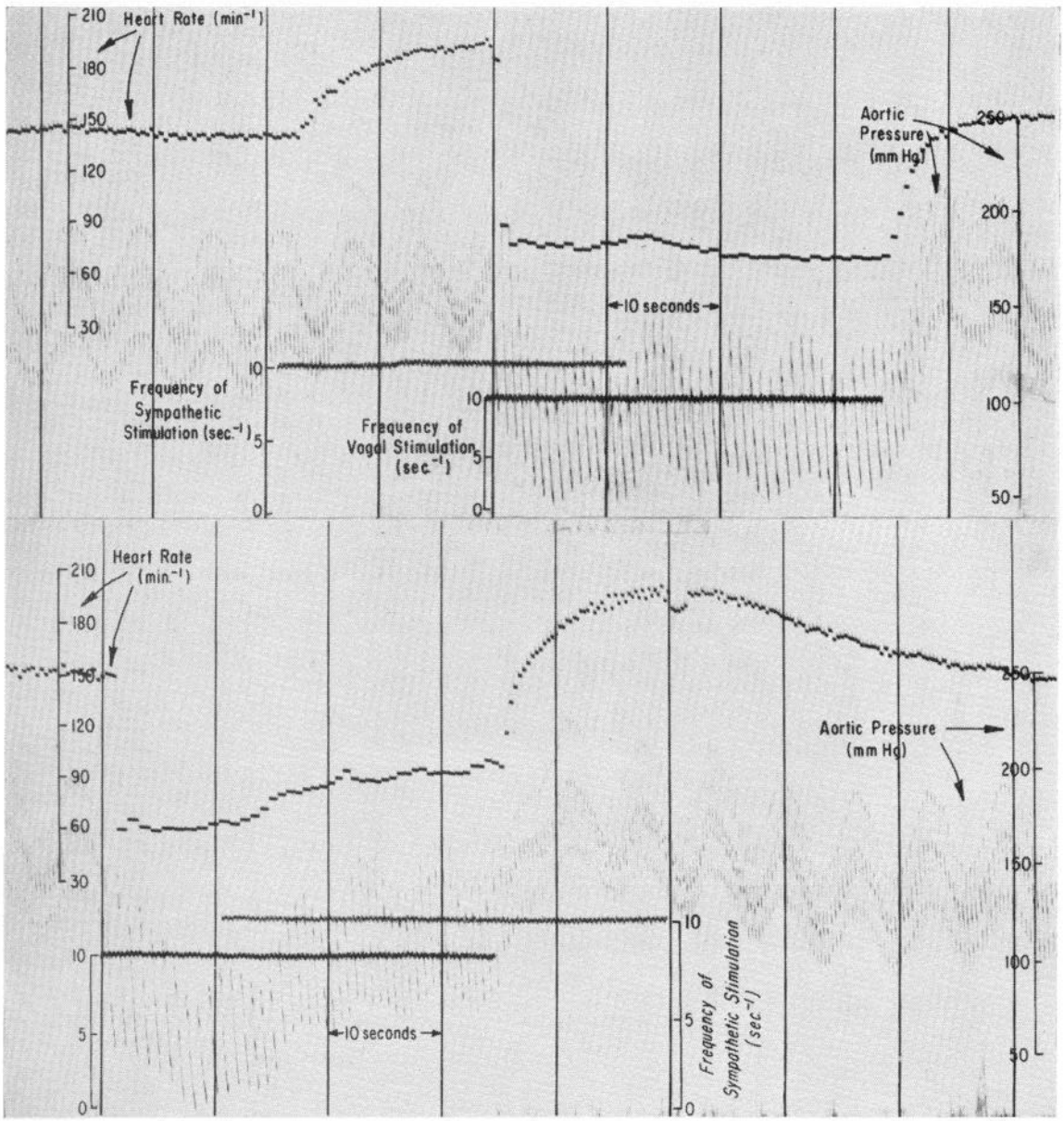


FIG. 11. Time course of heart rate and arterial blood pressure resulting from step increase and decrease in sympathetic and vagal stimulation.

link discussed in this paper may be an especially important determinant of the response of the circulatory system to an external disturbance since the observed lags of this system are relatively long.

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