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Effect of Combined Sympathetic and Vagal Stimulation on Heart Rate in the Dog

By Homer R. Warner, M.D., Ph.D., and Richard O. Russell, Jr., M.D.

ABSTRACT

A set of equations is described which permit prediction of the time course of heart rate in a dog anesthetized with pentobarbital from the time course of frequency of stimuli applied to the distal cut ends of vagus and sympathetic efferent nerves to the heart. These equations, although based on assumptions as to the physiological mechanisms involved, were only tested for their ability to describe the kinetic relationship involved. The time course of heart rate resulting from combined vagus and sympathetic nerve stimulation (HR_{sv}) is given by the equation:

$$HR_{sv} = HR_v + (HR_s - HR_0) (HR_v - HR_{min}) / (HR_0 - HR_{min}),$$

where the subscripted terms are heart rate values due to vagus stimulation (v), sympathetic stimulation (s), no stimulation (0) and the minimum (min) heart rate achievable by vagus stimulation alone. Clearly the vagus influence is capable of dominating the sympathetic in the control of heart rate.

ADDITIONAL KEY WORDS
computer nervous control

heart rate

cardiovascular control

■ The time course of heart rate resulting from stimulation of the sympathetic or of the vagus nerves to the heart is described by a mathematical model developed by Warner and Cox (1) in 1962. This model predicts the heart rate response to stimulation of either set of nerves alone but will not predict the response to simultaneous stimulation of sympathetic and vagus nerves. It is the purpose of this paper to describe an addition to the model which predicts the response to combined stimulation (2) and to describe experiments designed to test the performance of the model under a variety of stimulus parameters.

Methods and Procedure

The experiments were performed on 14 mongrel dogs anesthetized with pentobarbital, 30 mg/kg, iv. A cuffed endotracheal tube was inserted, and the animals were maintained on positive-pressure ventilation with 100% oxygen. A single-lead electrocardiogram was monitored on an oscilloscope throughout the procedure to assure that all measurements were made during a time when the animal had a normal sinus rhythm.

The isolation and preparation of the sympathetic and vagus nerves was performed as previously described (1). The distal cut ends of the vagus and cardiac sympathetic nerves (usually on the right side) were stimulated supramaximally with a 6-v, 1-msec square wave generated through a digital-to-analog converter by a Control Data 3200 digital computer and passed through an isolation transformer. Timing of each stimulus for either nerve was controlled by the program and the repetition rate varied from zero to 20/sec. In these experiments no attempt was made to control the timing of the stimuli with respect to the cardiac cycle. Data used to test the model were obtained by sampling heart rate (measured as the reciprocal of the R-R interval) once each second as well as the frequency of the stimulation of the vagus and the sympathetic nerves. The time course of heart rate and frequency of stimulation were plotted on a

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memory oscilloscope as the experiment proceeded and were stored on a magnetic disc for later testing of the mathematical model.

In each experiment the time course of the heart rate response to sympathetic stimulation alone was first determined by changing in a step-wise fashion the frequency of sympathetic nerve stimulation. From these data, values for parameters of the sympathetic portion of the model could be determined as described below. Following this, a similar procedure was performed using vagal stimulation alone to establish parameter values for the vagus model. This preparation, with sympathetic and vagus nerves to the heart severed, was very stable, and

repeatable responses could be obtained for as long as 6 hours.

After recording the responses to vagus and sympathetic nerve stimulation independently, the heart rate response to combined stimulation was determined by stimulation of these nerves over a wide range of frequencies (0 to 20/sec) and in various combinations. The model was tested by using the time course of frequency of vagal and sympathetic stimulation as forcing functions and comparing the solution of the model equations with the recorded time course of heart rate which represents the animal's response to these functions. These solutions were obtained on a Control Data 3200 digital computer which uses

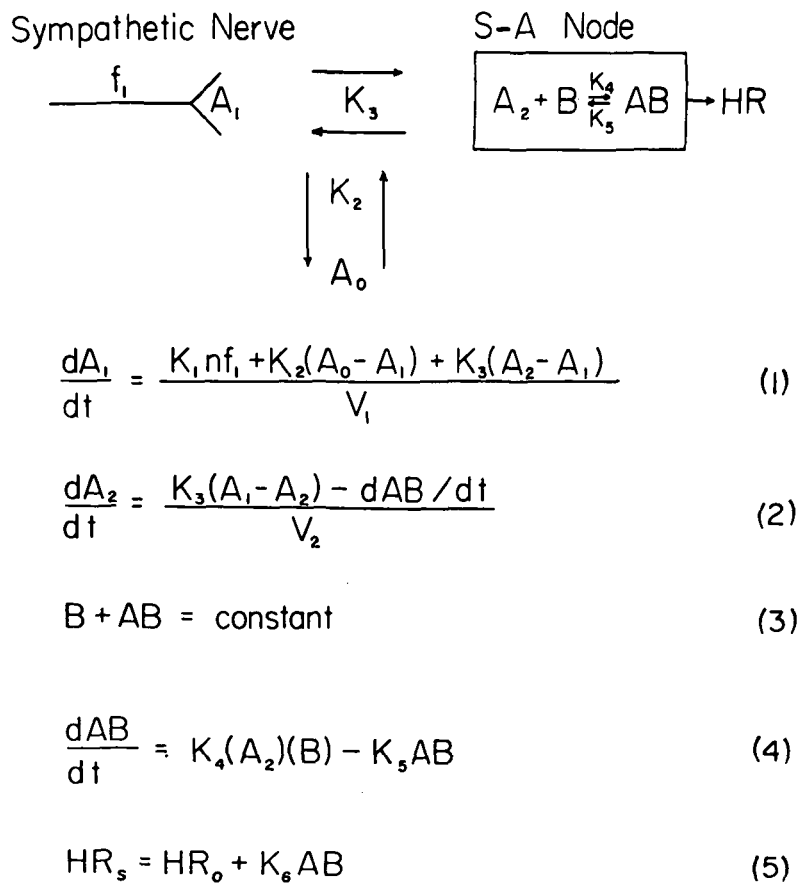


FIGURE 1

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 S-A 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.

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the MEDLAB time-sharing system developed in this laboratory (3) to permit the user to control his equation solution from a remote console. On this console, which consists of a memory oscilloscope and a set of 12 keys, solutions are plotted for comparison with the experimental data, and the experimenter may alter any parameter values prior to each new solution. He may specify which variables to plot and control horizontal and vertical scaling of each plot following each solution. Repeated parameter adjustments are made until an optimal fit (by visual examination) is obtained between the predicted and recorded time course of heart rate at those points on the curve that are most sensitive to the model parameter values as judged by visual examination.

Mathematical Model

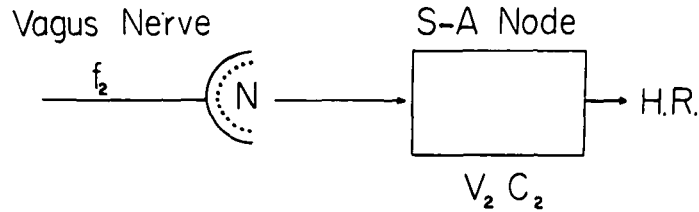
Before describing the effect on heart rate of combined stimulation of sympathetic and vagus nerves to the heart, it is first necessary to describe the relationship between the time course of heart rate and the time course of stimulation of sympathetic nerves (f_1) alone and vagus nerves (f_2) alone. Action potentials on the sympathetic efferent nerves to the heart cause release of norepinephrine at the S-A node. The rate of change of norepinephrine concentration in the immediate vicinity of the nerve endings (dA_1/dT) is determined by the relationship shown as equation 1 in Figure 1. K_1 is the amount of norepinephrine released per action potential, f_1 is the frequency of stimulation, and n is the number of nerve fibers stimulated when the stimulus is supra-maximal. The constant, K_2 , represents the rate of diffusion of water containing norepinephrine into and out of the circulating blood where the norepinephrine concentration is A_0 and K_3 represents diffusion to the active site on the S-A node cells where the norepinephrine concentration is A_2 . V_1 is the effective dilution volume for norepinephrine in the vicinity of the nerve ending.

The second-order reaction depicted by equations 2, 3, and 4 shows that the concentration of compound AB at any time depends upon the concentration A_2 of norepinephrine and the amount of the substance, B, which, it is postulated, is present in limited amounts and thus accounts for the observed

saturation effect when the sympathetic nerve is stimulated at increasing frequency. The heart rate due to the sympathetic stimulation alone (HR_s) at any time then will be determined by the initial heart rate when no sympathetic or vagal stimulation is present (HR_0) and the amount of this active compound (AB) which exists. Alternately, B could represent an active site at the S-A node on which norepinephrine must be adsorbed to affect heart rate or it could be an enzyme which must combine with the norepinephrine to produce the effect.

The model describing the relationship between the frequency of action potentials (f_2) on the cardiac vagus nerves and the behavior of S-A node is shown in Figure 2. These nerve endings are depicted as having vesicles which contain acetylcholine. As shown in equation 6, the rate of change of the number of vesicles, N , with respect to time, depends on two terms. The rate of regeneration of vesicles is proportional (K_7) to the difference between the number (N) existing at that time and the maximum number (N_m) when no stimulus has been present for some time. The rate of breakdown of vesicles is proportional (K_8) to the product of N and the frequency of stimulation. The rate of change of concentration of acetylcholine (C_2) at the S-A node is expressed in equation 7. The rate of increase in C_2 will depend upon the number of fibers stimulated (n), the fraction of vesicles discharged per action potential per stimulus per nerve fiber (K_8), the number of vesicles (N), the concentration of acetylcholine in the vesicles which is assumed constant (C_1) and the frequency of supramaximal stimulation of the vagus nerve (f_2). The rate of decrease in C_2 depends on the rate of hydrolysis of the acetylcholine by cholinesterase and is proportional (K_9) to C_2 . The effective volume of distribution of the acetylcholine at the S-A node is V_2 .

Equation 8 is a nonlinear function. The period of the heart cycle due to vagal stimulation (P_v) is equal to the period with no stimulation (P_0) plus an increment in period which is proportional (K_{10}) to the acetylcholine concentration in the node (C_2)



$$\frac{dN}{dt} = K_7(N_m - N) - K_8 N f_2 \quad (6)$$

$$\frac{dC_2}{dt} = \frac{nK_8 N C_1 f_2 - K_9 C_2}{V_2} \quad (7)$$

$$P_v = P_0 + K_{10} C_2 \text{ for } C_2 < a \quad (8)$$

$$P_v = \infty \text{ for } C_2 > a$$

$$HR_v = \frac{60}{P_v} \quad (9)$$

FIGURE 2

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 S-A 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.

as long as C_2 remains below some critical value, A . Any further increase in stimulation of the vagus nerve will cause a sudden cessation of action potentials at the pacemaker, here represented by P_v going to infinity. The heart rate due to vagal stimulation alone (HR_v) is defined by equation 9. The minimum heart rate achievable by vagal stimulation short of complete arrest (HR_{min}) is about 30/min.

The heart rate response (HR_{sv}) to stimulation of both sympathetic and vagus nerves to the heart in any combination of stimulus frequencies (F_1 and F_2) is described by: $HR_{sv} = HR_v + (HR_s - HR_0) (HR_v - HR_{min}) / (HR_0 - HR_{min})$ (10). No new parameters are

introduced by this equation, and all parameter values are determined from the heart rate response to stimulation of the sympathetic alone and the vagus alone. Notice that sympathetic effect on heart rate ($HR_s - HR_0$) is modified by a ratio of differences which approaches zero as the heart rate response to vagal stimulation alone approaches HR_{min} . Thus, at higher rates of vagal stimulation even maximal sympathetic activity will have little effect on heart rate. In the limit as vagal stimulation is discontinued, HR_v will equal HR_0 and this ratio becomes one. No explicit physiological basis for the relationship shown in equation 10 is postulated.

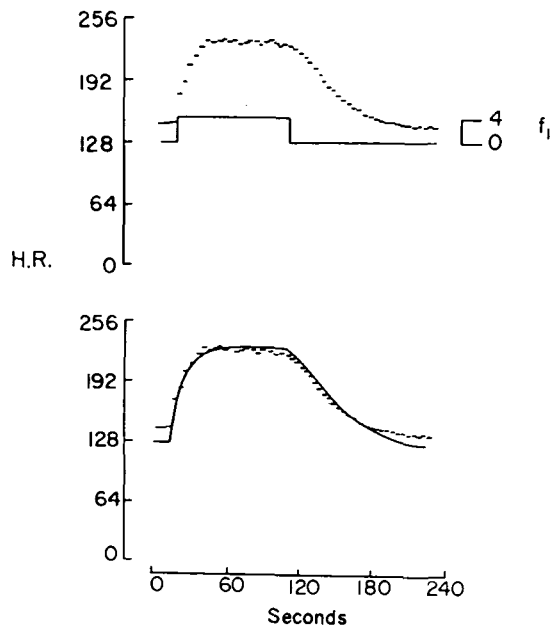


FIGURE 3

Top: The observed sympathetic response shown here is the upper line and the step increase in sympathetic stimulation is the lower line. Note the slower recovery of the heart rate than response with sympathetic stimulation. Bottom: The predicted heart rate from the model (solid line) is superimposed on the observed heart rate.

Results

The time course of heart rate in response to stimulation of the right sympathetic nerve alone is shown at the top of Figure 3. As stimulation is begun at 4/sec (onset of step function), heart rate, after a delay of 1.5 seconds, rises rapidly from 133/min to a new steady-state value of 220/min. Following a step-wise discontinuation of f_1 , again there is a delay of 1 to 2 seconds before heart rate begins to fall to its initial value before stimulation. The rate of decrease in HR_S is much slower than the rate of increase. In the lower panel of Figure 3 is shown this same heart rate response and superimposed on it (solid line) is the solution of the mathematical model which predicts HR_S from the time course of f_1 .

The heart rate response (HR_V) to vagal stimulation (f_2) is shown in Figure 4 using a similar format of data plotted on the face of a

memory oscilloscope. Two step functions in f_2 were used, the first from zero to 4/sec and the second from zero to 6/sec. In each case there is an immediate fall in HR_V with the onset of stimulation, in contrast to the relatively slow response to f_1 . Discontinuation of f_2 resulted in a rise in HR_V to its initial value which was slower than the fall in HR_V with the onset of vagal stimulation. There is no tendency for HR_V to return toward its control value during vagal stimulation if all sympathetic nerves have been severed. HR_V predicted by the mathematical model from the time course of f_2 is plotted in the lower frame again for comparison with the measured heart rate response.

In the same dog, sympathetic and vagus nerves to the heart were then stimulated in various combinations of f_1 and f_2 and the time course of HR_{SV} was compared to HR_{SV} predicted from the mathematical model using all ten equations with parameters obtained by fitting the predicted and measured heart rate response to f_1 and f_2 alone at any two step

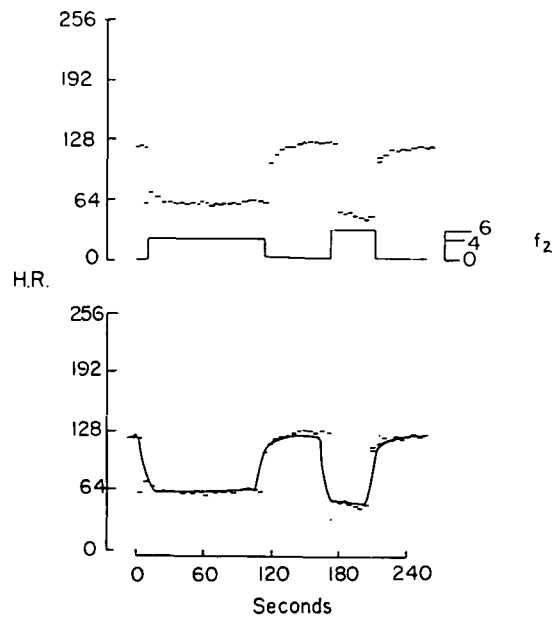


FIGURE 4

Top: The observed heart rate response to two step changes of vagal stimulation. Bottom: The predicted heart rate response is shown as the solid line for comparison with the observed response.

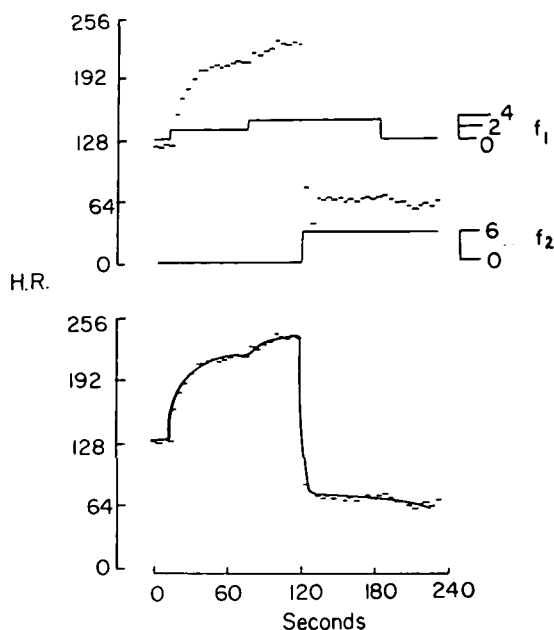


FIGURE 5

Top: Response to vagal stimulation (f_2) while sympathetic stimulation (f_1) is continuing. Bottom: Model prediction of heart rate response (solid line) compared to measured heart rate.

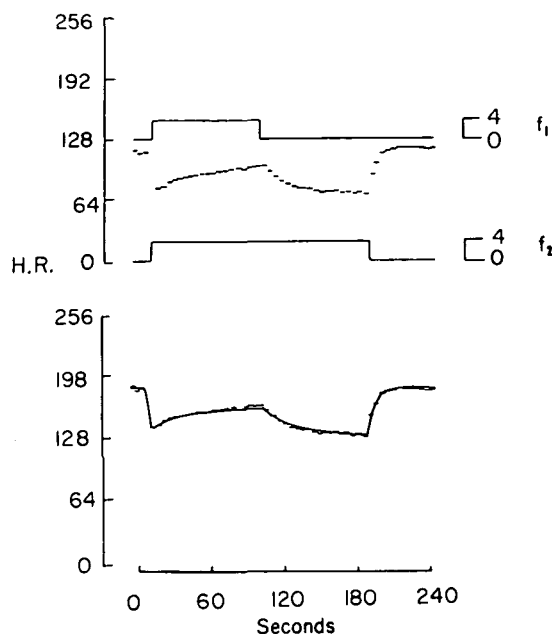


FIGURE 6

Top: Simultaneous stimulation of vagus and sympathetic nerves to illustrate the difference in response time. Bottom: Model simulation of above response using the same forcing functions.

functions. As shown at the top of Figure 5, f_1 was first begun at 2/sec and then increased to 4/sec. While f_1 was continued at this level, f_2 was begun at 6/sec resulting in an immediate fall in HR_{SV} from 230/min to 60/min within one heart cycle. When f_1 was discontinued, only a small further decrease in HR_{SV} occurred as the sympathetic effect slowly disappeared. Again the frame at the bottom shows a comparison of measured and predicted HR_{SV} .

In the experiment shown in Figure 6, f_1 and f_2 are begun simultaneously. Since the response to f_2 is much more rapid than the response to f_1 , HR_{SV} reaches its minimum value at once and then rises to its new steady state as the sympathetic effect gradually reaches its peak. When f_1 is discontinued, HR_{SV} falls slowly to the value obtained on the first heart beat following the onset of combined stimulation. Again the measured and predicted HR_{SV} are shown almost superimposed in the bottom frame.

Discussion

The mathematical model here presented should serve two useful purposes. First, it represents a quantitative relationship between the input and output of a very important component of the cardiovascular control system. Such information is essential in the building of more comprehensive models of cardiovascular control.

Secondly, this model provides a basis for extrapolation to other physiological states in which the time course of heart rate is changing in response to a changing environment. It is apparent, for instance, from these studies that any sudden change in heart rate within one or two heart beats cannot be brought about through direct effect of variations in frequency of sympathetic action potentials arriving at the S-A node. Furthermore, it is clear that at slow heart rates produced by vagal stimulation an increase in sympathetic activity will have little influence on heart rate. The converse of this is that the

observation of a slow heart rate does not preclude the presence of a high frequency of action potentials in the efferent sympathetic nerves to the heart.

The cervical vagus contains a variable number of sympathetic fibers. In an occasional experiment this sympathetic activity is apparent as an overshoot in heart rate following cessation of vagal stimulation which has all the characteristics seen with combined vagal and sympathetic activity. Because the response to discontinuing f_1 is very slow compared to f_2 , the two effects can be clearly separated. When such a response is seen in an experiment, the electrodes are re-adjusted in the nerve until a "pure vagal" response is obtained.

Finally, of course, it must be emphasized

that the mechanisms hypothesized to explain the behavior of the system cannot be shown to exist by the experiments performed here. It is hoped, however, that this quantitative description of the system performance may provide some useful constraints for the interpretation of other physiological experiments aimed at elucidating these mechanisms.

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