MODELING THE CAROTID SINUS BARORECEPTOR

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ABSTRACT A mathematical model that describes the relationship between sinus pressure and nerve discharge frequency of the carotid sinus baroreceptor is presented. It is partly based upon the single-fiber data obtained by Clarke from the sinus nerve of a dog. The model takes into account what is currently known about the physiology of the baroreceptor. It consists of two nonlinear ordinary differential equations and eight free parameters. With one set of values for these eight parameters, the model reproduces well the experimental results reported by Clarke for positive ramp pressure inputs. Only three parameters needed to be adjusted in order to fit the dynamic data. The remaining five were obtained from static and steady-state data.

INTRODUCTION

Attempts to describe quantitatively the functioning of the baroreceptors date back to Landgren's work (1952 *a*). In recent years several mathematical models for the baroreceptor have appeared in the literature (Christensen, 1967; Clarke, 1968; Franz, 1968; Levinson et al., 1966; Peterson, 1966; Poitras et al., 1966; Scher et al., 1967; Spickler and Kezdi, 1967; Spickler, 1968; Warner, 1958, 1965; Zerbst et al., 1970). All these models, with the exception of a few, are gross models intended to simulate the over-all relationship between pressure and nerve discharge frequency. They pay little or no attention to the structural details of the pressure sensor. Moreover, many of them are based upon multifiber data. Christensen (1967) and Franz (1968) are the only authors who used single-fiber data and who ever attempted to fit more than one set of experimental data with one set of values for the model parameters.

A model is proposed in this paper that takes into account the viscoelastic properties of the vessel wall and incorporates into it a steady-state relationship observed in Clarke's data (1968) for positive ramp pressure inputs. The electrical properties of the receptor are grossly lumped in a simple encoding process. It is based on the assumption that most of the dynamics arise in the mechanical components of the receptor. Validation of the model rests on its ability to reproduce well the experimental data reported by Clarke for positive ramp pressures. The description of the model is in terms of two nonlinear ordinary differential equations with eight free

parameters. Only three of these eight parameters needed to be adjusted to fit the dynamic data. Four of the other five were chosen optimally from the static data and the remaining one was determined from the steady-state portion of the dynamic data.

THE PROPOSED MODEL

The physiological components of a baroreceptor are shown in Fig. 1. This seems to be the best starting point for arriving at any realistic model for the baroreceptor. An input of the form shown in Fig. 2 A is ideally suited to studying the behavior of mechanoreceptors since the response to such an input exhibits the effects of both the stimulus and its time derivative in the beginning ($0 \leq t < t_1$) and those of the stimulus alone later ($t \geq t_1$). We shall henceforth refer to this input as clipped-off ramp input. The muscle spindle has been studied extensively by Ottoson and Shepherd (1965) using such inputs of stretch. The response of mechanoreceptors to this type of input is shown in Fig. 2 B. The salient features of the response are the overshoot at approximately the "shutoff" time t_1 and the two distinct phases of the off response, a rapid first phase followed by a slow decay.

Let us now try to trace the origin of the overshoot in the response of a baroreceptor to a clipped-off ramp input. We concluded that it cannot be in the first component shown in Fig. 1 from experiments carried out in our laboratory on the dynamic relationship between pressure and diameter of arteries. Cat's common carotid artery was used in these studies. The change in diameter was measured by shining a spot of light on the artery and measuring the amount of light reflected. The latter was picked off by a pair of photoelectric diodes that formed the opposite arms of a bridge circuit. No overshoot of the vessel diameter was observed to clipped-off ramp pressure inputs.

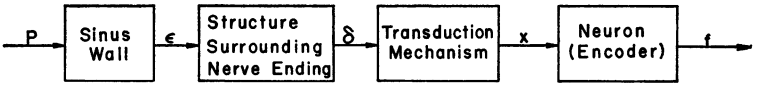

FIGURE 1 Block diagram showing the components of a baroreceptor. P, intrasinus pressure; ϵ, wall strain; δ, membrane strain or stress; x, generator current or potential; f, firing frequency.

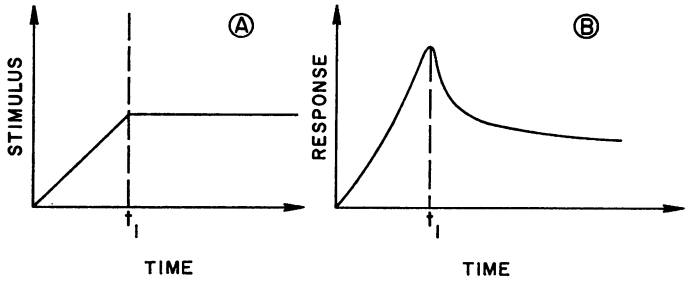

FIGURE 2 Response of a mechanoreceptor to a clipped-off ramp input.

That the overshoot cannot be in the encoder process is evident from the work of Lippold et al. (1960) on muscle spindles. By passing a step current in either direction along the muscle, they observed a corresponding step change in firing frequency. From this they concluded that adaptation had to be in the mechanical components of the spindle.

Many investigators who have attempted mathematical modeling of the muscle spindle have obtained the overshoot in the response by relating the total strain of the spindle to a strain at the receptor site by means of a viscoelastic coupling (Gottlieb et al., 1969; Houk et al., 1966; Toyama, 1966). That this is not the case has been shown by Ottoson and his coworkers (Husmark and Ottoson, 1971; Ottoson and Shepherd, 1968). It should be pointed out that the strain at the receptor site mentioned above is not the same as the variable δ in Fig. 1. δ represents a strain or a stretch on the receptor membrane itself.

From the above discussion it is concluded that the overshoot exhibited by baroreceptors must arise either in the intricate structural connection of the nerve ending to the vessel wall or in the transduction mechanism. It is hard to locate any more clearly the origin of the overshoot from what is currently known about stretch receptors. Therefore, it is necessary to make certain assumptions in order to proceed with the modeling. The assumption made here is that all the dynamics seen in the receptor response arise in the mechanical components of the receptor. This is, of course, questionable. It is justified only by the ability of the model to reproduce experimental results. Furthermore, we attribute the overshoot phenomena to the structural connection of the nerve ending to the vessel wall (the second component in Fig. 1) and relate x and δ by the following simple linear relation:

$$x = k\delta. \tag{1}$$

Many previous baroreceptor models have assumed a linear relationship between the variables f and x with a threshold and a fixed "jump" frequency (Clarke, 1968; Franz, 1968). Data of Landgren (1952 *a*) and Clarke (1968), however, show that the jump frequency, that is, the frequency of firing just past threshold, increases with the time derivative of pressure, dP/dt. The proposed model incorporates this effect by modeling the encoder process as follows: an impulse discharge is assumed to occur at time t_{i+1} if the following two conditions are satisfied.

$$x > x_{th}, \text{ the threshold value of } x, \tag{2a}$$

$$\int_{t_i}^{t_{i+1}} x(t)\, dt = A_r, \tag{2b}$$

where t_i is the instant of occurrence of the preceding impulse, and A_r is a constant. Clearly the idea here is that a firing is triggered if and only if the accumulation of a certain physiological quantity exceeds a certain threshold level.

We shall now focus our attention on modeling the mechanical components of the baroreceptor. Regarding the structural connection of the nerve ending to the vessel wall, very little is known. Whatever we know is far from adequate to enable us to arrive at a meaningful functional relationship between the variables ϵ and δ. On the other hand a great deal more is known about the mechanical properties of the sinus wall. We shall therefore discuss the modeling of the sinus wall first. After determining the mathematical description of the sinus wall properties, we shall attempt to derive the relationship between ϵ and δ on the basis of the over-all properties of the baroreceptor.

It is now known that the sinus wall has very few smooth muscle fibers and is composed mostly of elastin and collagen. As the intrasinus pressure is increased, tension develops first in the elastic fibers. Collagen fibers, which are less distensible than the elastic fibers, develop tension at higher pressures resulting in a reduction of the slope of the pressure-strain curve.

The static pressure-strain relationship can be adequately represented by two straight lines as has been done by Clarke (1968). Such a representation will have three parameters, two slopes and a break point. The discontinuity in the slope may present certain analytical difficulties and it may be necessary to incorporate a smooth transition of slopes. In fact, this is what Clarke did in his model.

The work published by King (1946) on the pressure-volume relation of elastomeric cylinders more than two decades ago provides an analytic expression for the pressure-strain relationship of the sinus wall.

$$A\sqrt{\frac{r_0}{r}}\left[\frac{\mathcal{L}^{-1}(\beta r/r_0)}{\mathcal{L}^{-1}(\beta)} - \frac{r_0}{r}\right] = P, \tag{3}$$

where P is the intrasinus pressure (relative to outside), r is the radius of the sinus at pressure P, r_0 is the radius of the sinus when $P = 0$, A, β are constants, and $\mathcal{L}^{-1}$ is the inverse Langevin function. The Langevin function $\mathcal{L}(z)$ is defined as follows:

$$\mathcal{L}(z) = \coth z - \frac{1}{z}. \tag{4}$$

Now, the strain ϵ is defined as:

$$\epsilon = \frac{r - r_0}{r_0}. \tag{5}$$

From equations 3 and 5 we obtain,

$$\frac{A}{\sqrt{\epsilon + 1}}\left[\frac{\mathcal{L}^{-1}\{\beta(\epsilon + 1)\}}{\mathcal{L}^{-1}(\beta)} - \frac{1}{\epsilon + 1}\right] = P. \tag{6}$$

King's derivation is based on the principles of statistical thermodynamics. Although

he had to make certain simplifying assumptions concerning the molecular chains of elastomers, his results describe remarkably well the behavior of aorta under static conditions. Moreover, he could relate the parameter β to age and thus interpret the aging process of aortas.

Equation 6 gives the static pressure-strain relation of the sinus wall in the proposed model. Notice that it has only two parameters, namely A and β. In using equation 6 we have made the assumption that the carotid sinus is perfectly elastomeric and has a circular transverse cross section.

The behavior of the sinus wall is characterized in our model by a nonlinear spring acting in parallel with a linear viscous element as shown in Fig. 3. Thus, the complete equation for the pressure-strain relation is:

$$C\frac{d\epsilon}{dt} + \frac{A}{\sqrt{\epsilon+1}}\left[\frac{\mathcal{L}^{-1}\{\beta(\epsilon+1)\}}{\mathcal{L}^{-1}(\beta)} - \frac{1}{\epsilon+1}\right] = P(t), \qquad (7)$$

where C is the viscosity coefficient.

The adequacy of a first-order differential equation with a linear viscous term is supported by the findings of Peterson et al. (1960). They reported that for small strains the pressure-strain relations are adequately described by a first-order linear differential equation with constant coefficients. It can be shown that equation 7 reduces to a constant coefficient linear equation for ϵ much smaller than one. For large strains, however, blood vessels exhibit nonlinear properties Preliminary studies in our laboratory on the viscoelastic properties of blood vessels indicate that a first-

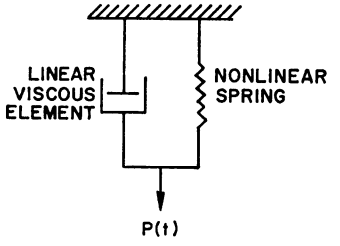

FIGURE 3

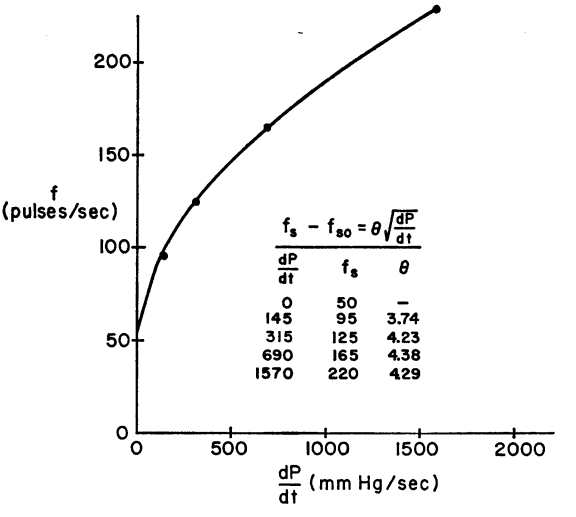

FIGURE 4

FIGURE 3 Model of the sinus wall.

FIGURE 4 Steady-state relationship between dP/dt and the firing frequency.

order differential equation sufficies to describe the pressure-strain relations. Whether or not the viscous term is linear is not clear and needs further investigation.

It now remains to obtain a mathematical representation for the second component in Fig. 1. It should include the steady-state relationship between the firing frequency and the time derivative of pressure that we observed in the experimental data published by Clarke (1968). Equation 8 below gives this relationship (see Fig. 4).

$$f_s - f_{s0} = \theta \sqrt{\frac{dP}{dt}}, \tag{8}$$

where f_s is the saturated firing frequency for a positive ramp pressure input, f_{s0} is the saturated firing frequency under static conditions $dP/dt = 0$), and θ is a constant.

Evidently the rate of strain $d\epsilon/dt$ contains information on the time derivative of pressure dP/dt. Therefore, the above steady-state relation can be incorporated by relating δ, the membrane strain or stress, and ϵ as follows:

$$\delta = \epsilon + \lambda g(\epsilon)\, d\epsilon/dt, \tag{9}$$

where λ is a constant.

The above equation was used in our initial model studies. The function $g(\epsilon)$ was obtained by differentiating the left-hand side of equation 7 and making certain approximations such as ignoring the term $C(d^2\epsilon/dt^2)$ since its contribution was small. Thus, the term $g(\epsilon)(d\epsilon/dt)$ was made proportional to dP/dt and equation 8 was satisfied. With this representation, however, it was not possible to get one set of parameter values to fit all of Clarke's data for positive ramp pressure inputs. Moreover, the functional form of $g(\epsilon)$ was not simple enough to lend itself to any interpretation.

Alternatively one could model the mechanical components of the baroreceptor as shown in Fig. 5. The variables ϵ_d and dP/dt are related by the following equation:

$$C_d \frac{d\epsilon_d}{dt} + \epsilon_d^2 = \sigma\, dP/dt. \tag{10}$$

Observe that the steady-state relation given by equation 8 is satisfied. Although this is not the only way equation δ can be satisfied, it is the most plausible one in our view. ϵ_d is a strain unrelated to the wall strain ϵ. δ is now given by

$$\delta = \epsilon + q\epsilon_d. \tag{11}$$

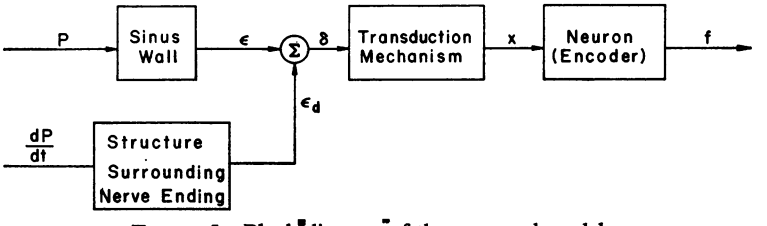

FIGURE 5 Block diagram of the proposed model.

Equations 1, 7, 10, and 11 now constitute part of the model. Equation 2 gives the necessary conditions for a nerve impulse to occur. The firing frequency at time t_i is taken to be the reciprocal of the interval time $(t_i - t_{i-1})$ where t_i's are the instants of occurrence of impulse discharge.

There are nine parameters associated with the above model: k, c, A, β, C_d, σ, q, x_{th}, and A_r. The parameter k can be eliminated by redefining x_{th} and A_r. Similarly q can be eliminated be redefining C_d and σ. Thus we have only seven free parameters. Simulation studies indicated certain modifications of equation 10 which are discussed in the next section.

RESULTS

Equation 6 which describes the static pressure-strain relationship was used to fit Landgren's data (1952 *b*) taken from the carotid sinus of cats. The results are shown in Fig. 6. It should be mentioned that the accuracy in the measured values of diameter is poor because of the tambour technique that Landgren used. The data clearly indicate that the saturation of the wall strain is a factor to be reckoned with in any realistic model of the baroreceptor.

In the simulation studies with Clarke's data (1968), the numerical values for the

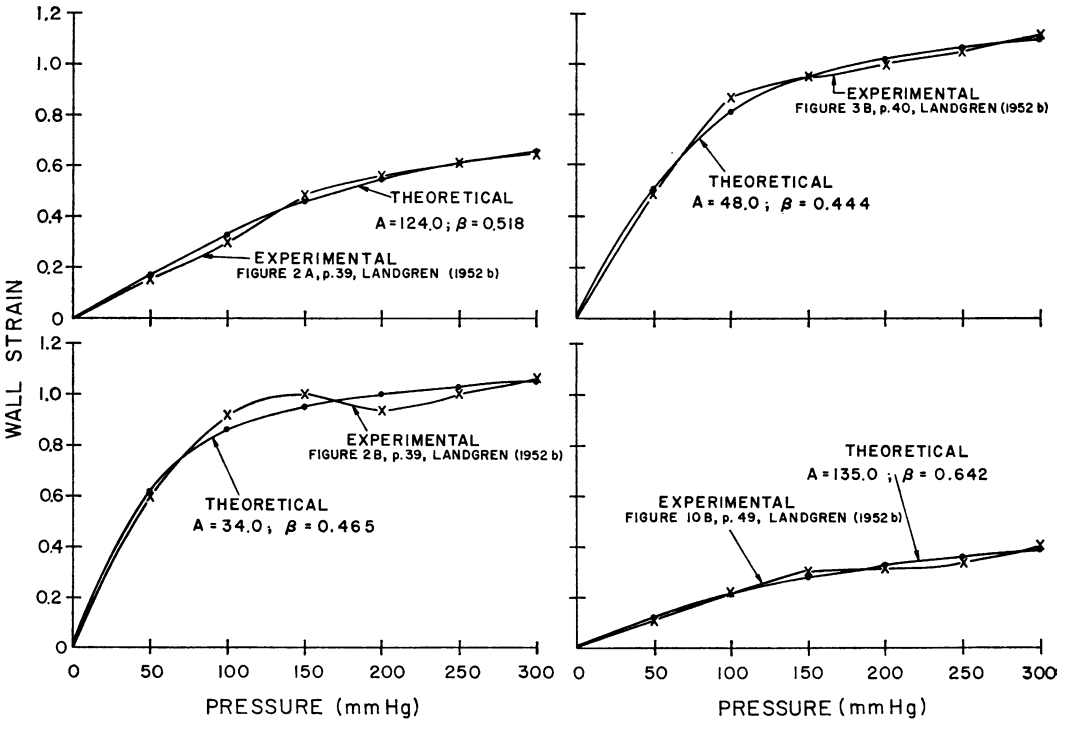

FIGURE 6 Pressure-strain relationship. Least square fit to Landgren's (1952 *b*) data. The values of A and β shown are optimal.

parameters A, β, x_{th}, and A_r were first determined optimally (in a least square sense) to fit the static pressure vs. firing frequency curve. The result is shown in Fig. 7. Although lower values of β gave a better fit at the knee portion, it resulted in values of ϵ exceeding its physiologic limit which is about 1.2 as judged from Landgren's data (1952 *b*). Clarke observed lower values of firing frequency when he decreased the pressure from 300 mm Hg in successive steps. For example, at about 125 mm Hg the firing frequency was only 29 while the pressure was being decreased as opposed to 40 while it was being increased. The hysteresis that he noticed is in contradiction to Landgren's findings. In view of this, no attempt was made to refine any further the model's fit to the static characteristic.

Next the value of σ was computed from the steady-state relationship given by equation 8. The parameters C and C_d were then adjusted to fit Clarke's data for positive ramp inputs. The response was found to be more sensitive to variations in C_d. It was necessary to vary C_d as a function of dP/dt in order to fit all the ramp input data with one set of parameter values. The variation of C_d with dP/dt is

$$C_d = \frac{C_{d0}}{1 + \gamma \frac{dP}{dt}}. \tag{12}$$

The results are shown in Fig. 8. All computations were done on a PDP-12 machine. Fourth-order Runge-Kutta method was used for integration. The parameter values are:

$$A = 84.0, \qquad \sigma = 0.008924,$$
$$\beta = 0.4, \qquad C = 2.0,$$
$$x_{th} = 0.483391, \qquad C_d = 0.667,$$
$$A_r = 0.022492, \qquad \gamma = 0.0046.$$

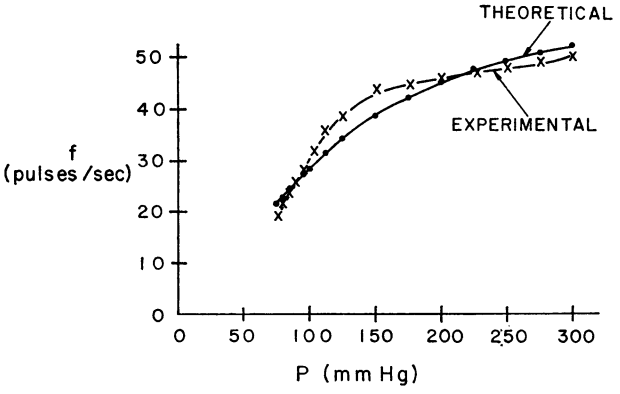

FIGURE 7 Pressure vs. firing frequency; static response.

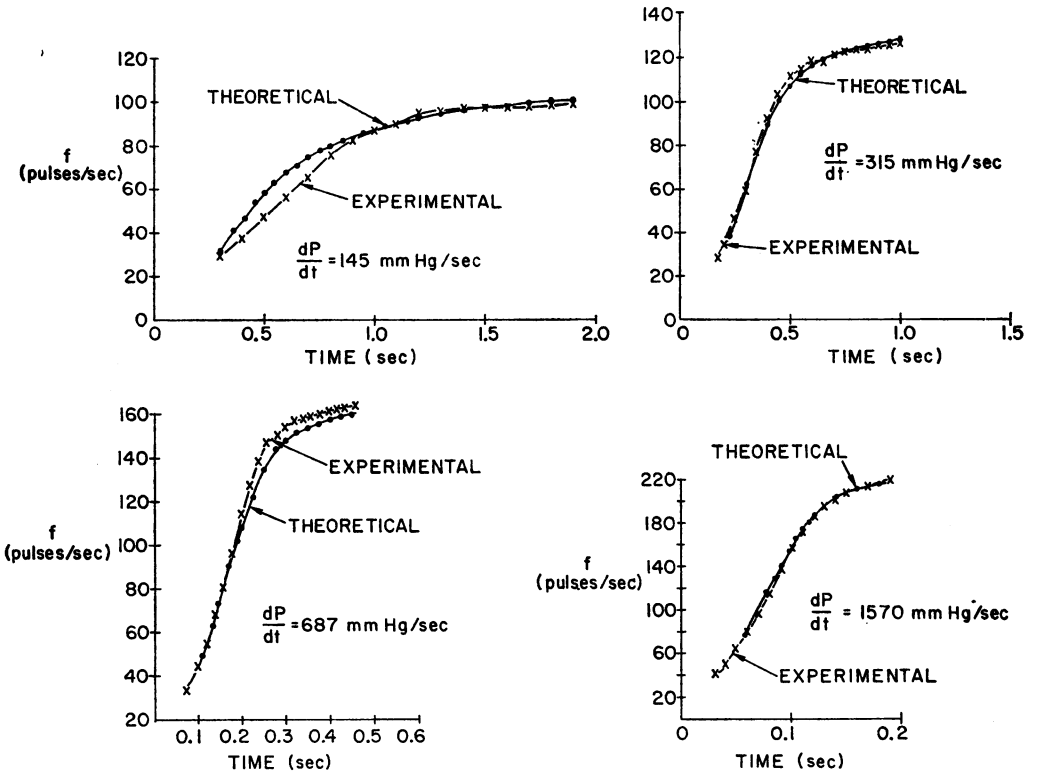

FIGURE 8 Dynamic response of the baroreceptor to ramp pressure input.

The instant at which the first fiiring occurs does not match very well with the experimentally observed value. This is because of the gross representation of the electrical properties of the receptor.

Finally equations 10 and 11 were modified as follows to take into account negative dP/dt.

$$C_d \frac{d\epsilon_d}{dt} + \epsilon_d^2 = \sigma \left| \frac{dP}{dt} \right|, \tag{13}$$

$$C_d = \begin{cases} \dfrac{C_{d0}}{1 + \gamma \left| \dfrac{dP}{dt} \right|} & \text{if} \quad \dfrac{dP}{dt} \geq 0, \\ -\dfrac{C_{d0}}{1 + \gamma \left| \dfrac{dP}{dt} \right|} & \text{if} \quad \dfrac{dP}{dt} < 0. \end{cases} \tag{14}$$

The variation of C_d with dP/dt is shown in Fig. 9.

With the above functional form for C_d, the model's responses were compared with Clarke's results for negative ramp inputs. In all cases except one ($dP/dt = -563$ mm

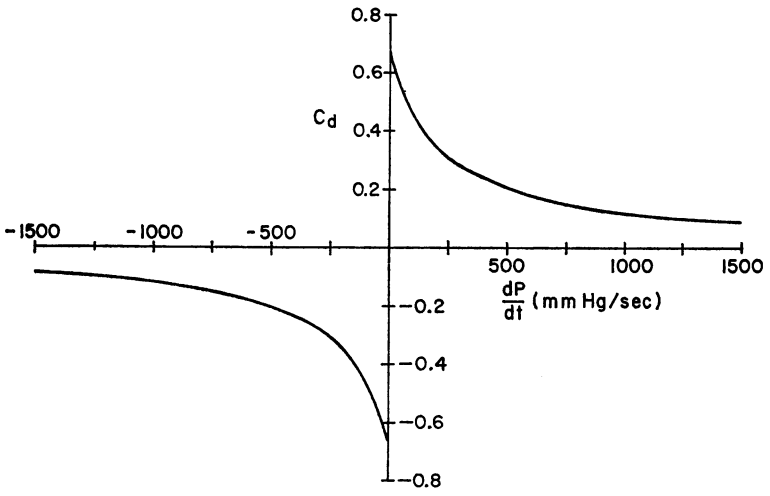

FIGURE 9 Variation of C_d with dP/dt.

Hg/sec) there was good agreement of shutoff frequency, the firing frequency just before the receptor stopped firing. For example, at a negative rate of change of pressure of 293 mm Hg/sec the model's shutoff frequency was 39.2 pulses/sec compared with the experimental value of 35.8 pulses/sec. The minimum value of the magnitude of dP/dt that would result in an immediate shutoff after the change of pressure was calculated assuming that a pulse occurred just before the application of input. The calculated value of 550 mm Hg/sec compares well with the experimental values reported by Clarke (1968) and Langren (1952 *a*), about 600 and 500 mm Hg/sec respectively.

DISCUSSION

The baroreceptor model presented here breaks down the sensor into four physiological components. Mathematical description of the functioning of each component is sought based on what is presently known about it and also on the over-all relationship between pressure and firing frequency. Much use has been made of the conclusions arrived at from experiments on muscle spindle. The approach taken here is more important than the results themselves in that it provides a framework for further work. Clarke (1968) took a similar approach but he could not reproduce the experimental observations with his equations.

In our model, ϵ_d is a strain experienced by the nerve ending only and is caused by the rate of change of pressure. The significance of a dP/dt input is not clear at the moment. ϵ_d may be caused by the slipping past one another of the adjacent layers of the sinus wall surrounding the nerve ending. It might be possible to derive a relationship between a membrane strain and rate of change of pressure based on the above idea.

δ which is defined as the total strain on the nerve ending may be thought of as the sum of components of the strains ϵ and ϵ_d. We cannot say anything more about how the two components should be combined unless we can derive the relationship between ϵ_d and dP/dt.

In any extension of the present model, the description of the components 1 and 4 in Fig. 1 need not be changed. Since we found C to be a relatively insensitive parameter, equation 7 is quite adequate to describe the pressure-strain relationship of the sinus wall. The encoder process we have used seems to be a good way of lumping the electrical properties of the receptor.

The weakest link in the model is the description of the transduction mechanism by a simple linear relation. This became evident from the response of the model to a clipped-off ramp input. The response did not show two discernible decay components past shutoff of the ramp. It showed only one slow decay. That the decay properties of the receptor are manifested in the transduction mechanism has been pointed out by Ottoson and Shepherd in a recent paper (1971).

It is well known that change in membrane conductance is one of the factors involved in the elicitation of electrical changes. Clarke (1968) arrived at a first-order linear differential equation with time-varying coefficients for the transduction mechanism by assuming the membrane conductance to be a function of the membrane strain. Zerbst et al. (1970) have used a similar idea in their model. It therefore seems plausible that the following equation will adequately characterize the transduction mechanism of the receptor:

$$\tau \frac{dx}{dt} + x = h\left(\delta, \frac{d\delta}{dt}\right), \tag{15}$$

where h $(\delta, d\delta/dt)$ is a function of δ and $d\delta/dt$.

C_d need no longer be a function of dP/dt. If we leave C_d a constant and characterize the function h with a single parameter, we will have nine free parameters in all for the complete model. Hopefully the model will then be able to reproduce with a single set of parameter values the experimental data for all the three types of inputs, namely, positive ramp, negative ramp, and clipped-off ramp. Our model studies are currently being continued in this direction.

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