In conclusion, we would like to restate our view that $V_{\text{max}}$ remains a valuable tool for studying sodium channels, particularly when investigators squarely face the likelihood that upstroke velocity is a nonlinear lens through which one may view available sodium conductance. Of course, there remains room for some to hope that, under certain conditions, the nonlinearity will be relatively mild. However, we feel the burden of proof has shifted significantly in light of our experiments and simulations and complementary results from other investigators (Fig. 1). The safest approach at present is to reckon with a strongly nonlinear relationship in individual cardiac preparations until evidence is provided to the contrary.

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Comments on

"Carotid Sinus Baroreceptor Reflex Control and the Role of Autoregulation in the Systemic and Pulmonary Arterial Pressure-Flow Relationships of the Dog"

which appeared in

Circ. Res. 54: 674–682, 1984

In their important and critical paper, Shoukas et al. (1984) studied the influence of the carotid sinus baroreceptor reflex on the entire systemic and pulmonary arterial pressure-flow relationships to understand better the reflex regulation of systemic and pulmonary vascular resistances. The definition of total peripheral resistance assumes a major role in this context. For the entire systemic arterial bed, total peripheral resistance (R) is classically defined as the ratio of mean arteriovenous pressure gradient [mean arterial pressure minus mean venous pressure (P) to cardiac output (Q)].

$$R = \frac{P}{Q}. \tag{1}$$

According to Shoukas et al., this equation assumes that pressure-flow relations are linear, i.e., $\Delta P/\Delta Q$ is constant at any range of flow or pressure, and the pressure at zero flow equals zero. On the basis of the finding that in the baroreflex-regulated vascular bed the P-Q curve is nonlinear and that zero flow occurs at a pressure above zero, Shoukas et al. seem to question the validity of Equation 1 to compute total peripheral resistance. How then does one compute peripheral resistance?

Figure 1 shows four kinds of possible arterial pressure-flow relationships. The P-Q relationship in panel A is a straight line which passes through the origin of both axes, the origin of the pressure axis being equal to mean central venous pressure (Pv). In this case, linear Equation 1 is valid, and the resistance is the same at any level of pressure or flow. If the P-Q relation is a straight line, and mean arterial pressure minus mean venous pressure at zero flow is not zero (panel B), the definition of total peripheral...
resistance should be modified to:

\[ R = (P - P_o)/Q. \]  

(2)

This is equivalent to moving the origin of the pressure axis from \( P_o \) to \( (P_v + P_o) \); the pressure-flow relationship is still linear and the resistance is the same at any level of pressure or flow.

When the P-Q relationship is nonlinear and passes through the origin of both axes (panel C), one can still calculate total peripheral resistance "at a given steady state," on the basis of Equation 1. In this case, however, we have to recognize that the value expressed as peripheral resistance represents a straight pressure-flow relationship passing through the origin of both axes and the point on the curve at "that steady state." When pressure (or flow) changes, the value of the calculated resistance also changes because of the change in slope of the straight line from the origin to the new steady state point on the curve. The change in slope reflects the nonlinearity of the P-Q relationship. The same reasoning can be repeated when the P-Q relationship is nonlinear and pressure at zero flow is not zero (panel D). According to Equation 2, absolute levels of total peripheral resistance during "steady states" at various points on the P-Q curve are equal to the slopes of the straight lines which connect that given point on the P-Q curve to \( P_o \) on the pressure axis. If the zero flow pressure intercept is small [as found in the closed-loop baroreflex control system by Sagawa and Eisner (1975) and Burattini and Borgdorff (1984)], the classical calculation of total peripheral resistance (Eq. 1) is acceptable.

Thus, Equation 1 gives a complete representation of the mean pressure-mean flow relation of the entire systemic arterial bed with constant peripheral resistance when zero flow pressure does not exist (or is negligible). If \( P_o \) is not negligible, Equation 2 holds. When the P-Q relationship is not a straight line and vascular resistance changes because of neural reflexes or other influences, Equation 1 (or 2) does not describe the entire pressure-flow relationship but is valid for calculating the absolute level of total peripheral resistance at any given steady state.

It is important to agree on these considerations in order to set up a mathematical model of the baroreflex control of total peripheral resistance which predicts mean pressure as a function of mean flow and is characterized by parameters which have clear physiological meaning. The quadratic or third-order polynomials which Shoukas et al. used to fit their measured pressure and flow data may be seen as a possible mathematical model. Unfortunately, the parameters (polynomial coefficients) of the model have no clear physiological meaning, which is a necessary condition for validation of models (Yates, 1978). In other words, the fundamental purpose of a model beyond the simple fit of measured data is the identification of functions which have clear physiological meaning.

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References


INDEX TERMS: Baroreflex regulation • Mathematical model • Peripheral resistance

Reply to the Preceding Letter

We appreciate Dr. Burattini's comments on our manuscript published in Circulation Research 54: 674–682, 1984. Dr. Burattini makes two totally separate points in his letter. The first concerns the applicability of the traditional calculation of total peripheral resistance (TPR) by either of his equations (1 or 2). The second point concerns the more general
Comments on "Carotid sinus baroreceptor reflex control and the role of autoregeluation in the systemic and pulmonary arterial pressure-flow relationships of the dog".

R Burattini

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