A Nonlinear Property of the Renal Autoregulation

In a series of experiments using controlled perfusion of the renal artery of dogs with arterial blood we found that the basic dynamics of the renal autoregulatory response can be described by a relatively simple second order transfer function[1-3]. In order to examine the validity of this linearization we compared the vascular reaction to different pressure or flow input pattern. We could show that the pressure response to flow steps, and vice versa, corresponds well with the prediction as calculated from the linear transfer function which was measured by using sinusoidal inputs of different frequencies[1,2]. In contrast, we found consistently in 15 experiments in anesthetized dogs that the pressure response to short flow pulses could not be predicted from the linear transfer function.

In the following discussion the characteristic pressure response to a flow pulse in the renal artery is demonstrated. A simple analog simulation is presented to explain the effect and the reason for the deviation from linearity. The recording from one experiment in the upper part of Figure 1 shows the following two characteristic and highly reproducible features: 1. A short flow pulse produces a corresponding pressure pulse and thereafter a long lasting pressure response. After the pulse the pressure rises slowly to a peak and then, very slowly, declines towards the control level. 2. The pressure response to a second impulse within the next two or three minutes is much smaller. The full response may be elicited again only after a control period of about 10 min. This basic pattern is independent on the control flow and pressure level.

According to the linear transfer function as measured from sinusoidal perfusion only a very small pressure response, similar or even smaller than the second response in Figure 1, would have been expected. Actually the latter type of response was found in all other arterial beds examined so far (femoral, mesenteric, coronary).

Since the characteristic first response, as shown in the upper part of Figure 1 closely resembles the pressure reaction to a positive flow step[2], the following way to simulate and explain the effect was chosen.

$$\frac{\triangle P}{Z \triangle \dot{Q}} = \frac{1 + \frac{3}{1 + 5s}}{1 + \frac{3}{1 + 200s}} \quad (1)$$

represents an example of the linearized and normalized input impedance of the renal artery in the low frequency region. Z is the setpoint of the impedance around which small changes are examined[1,2], s is the complex frequency. In the following simulation the value 1 is chosen for Z. Eq. 1 is represented within the dashed square in Figure 2. To explain the pulse response it is assumed that the flow pulse generates within the vascular system of the kidney an 'activated state' which, after the pulse, only slowly declines. The slow pressure reaction then is a response to the step increase of the 'activated state'. This mechanism is represented in Figure 2 by the integrator I, which is

[1] Th. Kenner and K. Ono, Experientia *27*, 528 (1971).
[2] Th. Kenner and K. Ono, Pflügers Arch. *324*, 155 (1971).
[3] Th. Kenner, Kybernetik, in print.

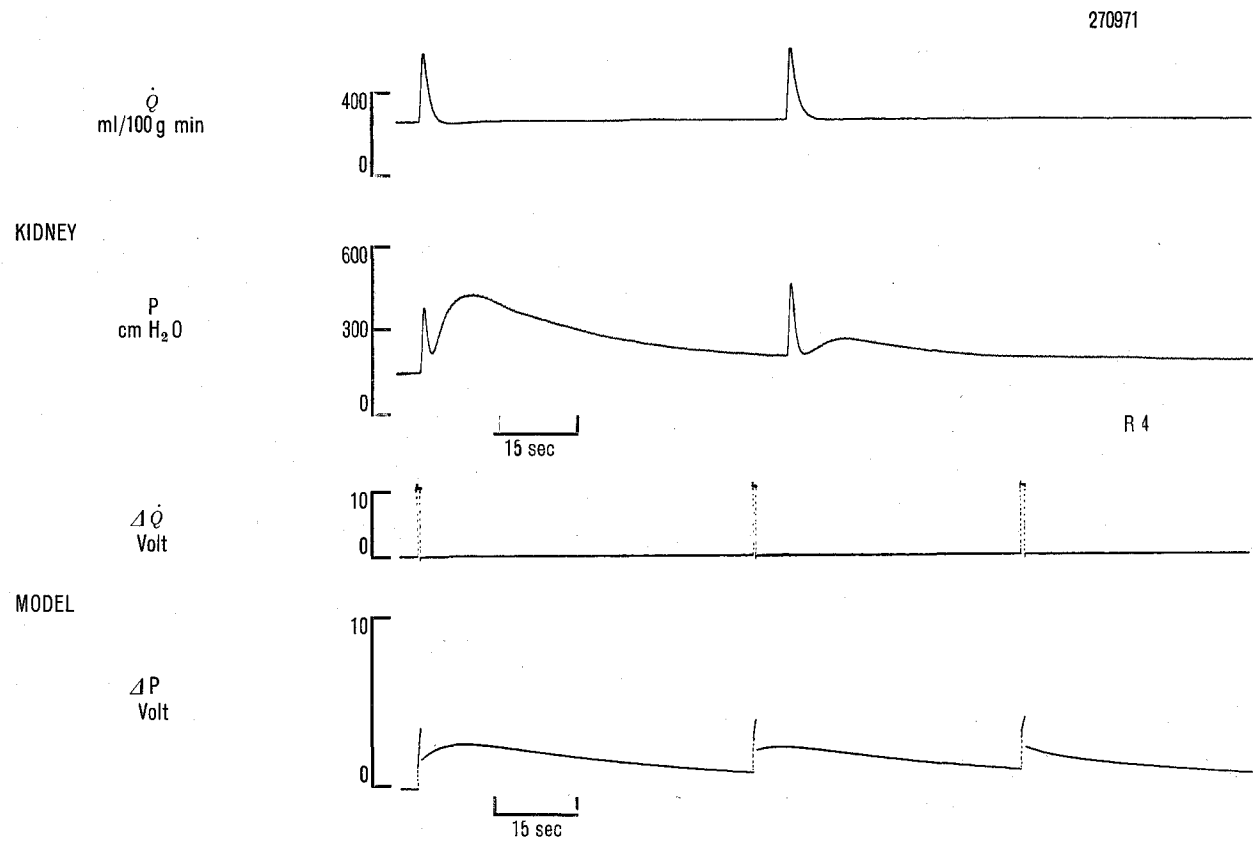

Fig. 1. Upper tracing. Flow ($\dot{Q}$) and pressure (p) in the renal artery (denervated) of an anesthetized dog. The artery was perfused by a controllable peristaltic pump with arterial blood. The record shows the characteristic pressure response to 2 successive flow pulses. Lower tracing. Analog simulation performed on a TR 48 analog computer. The program used is shown in Figure 2.

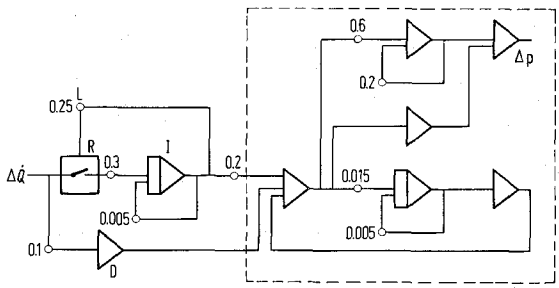

Fig. 2. Analog circuit to simulate the pressure response in the renal artery (Δp) to flow inputs ($\Delta \dot{Q}$). The dashed square represents the linear part of the transfer function; see eq. 1 in the text. The rest of the circuit represents the nonlinear element as explained in the text. The numbers refer to the potentiometer settings.

charged during the pulse and only slowly decharges after the pulse with a time constant of 200 sec (in the given example). The direct effect of the pulse goes via amplifyer D. When the integrator output (i.e. the 'activated state') reaches a certain level, provided by potentiometer L, relay R switches the input to the integrator off.

The simulation was performed on a TR 48 analog computer. The effect of the nonlinear element can be seen in the lower part of Figure 1. The first response corresponds to the summation of the pulse response and the response to the square input of the 'activated state'. If a 2nd pulse is provided before the 'activated state' has declined to Zero, the response will be much smaller. The 3rd pulse in Figure 1 (lower part) is still shorter after the previous pulse. Therefore, nearly no change in the 'activated state' is produced by the pulse and the reaction corresponds to the response which would be expected from the linear model. In a quite similar way, examining sinusoidal inputs, the results provide information only about the linear part of the system as long as the integrator (the 'activated state') continues to be fully charged.

The following conclusions can be drawn: 1. We have found a unique response to short flow pulses in the denervated renal arterial bed of anesthetized dogs. The response was found alike in kidneys left in situ, in autotransplanted and isotransplanted kidneys. 2. Although an explanation of the basic underlying mechanism cannot be given, a simple simulation suggests the generation by the pulse of an 'activated state' in the renal vascular bed, which might be a myogenic or humoral phenomenon. 3. The results are a step towards the explanation of long term effects of certain experimental procedures, and possibly of the influence of pulsatile pressure on the renal arterial bed[4].

Zusammenfassung. Die A. renalis von Hunden wurde mit arteriellem Blut mittels einer peristaltischen Pumpe durchströmt. Wir fanden hierbei eine bemerkenswerte Druckantwort auf kurze Strömungspulse, die spezifisch für die Niere zu sein scheint. Eine anschauliche Deutung der Reaktion konnte mit Hilfe einer einfachen Analogsimulation gegeben werden.

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Humoral Autoregulation of Blood Flow and Blood Pressure

In previous publications[1-3] we have shown that the reaction of the local arterial impedance of different arterial beds to changes in pressure or flow basically can be described as interaction between two processes. These were tentatively called autoregulation of flow and autoregulation of pressure[1]. To describe the interaction of both processes, which ususally have different time constants, we used the germ reciprocal autoregulation. In the following discussion we will show that besides by intrinsic mechanisms both autoregulation of flow and of pressure can be achieved by humoral mechanisms.

For a simplified explanation of this concept it may be assumed that no control or intrinsic autoregulatory mechanism exists in a local arterial bed, except for the presence of a vasoactive substance in concentration X in the arterial blood stream. In this example the input impedance Z (we prefer this symbol to the previously used R_i) of the arterial bed thus is a function of X only. p and $\dot{Q}$ are input pressure and flow, all variables are frequency dependent. The input impedance then is defined as

$$Z(X) = p/\dot{Q}\,. \tag{1}$$

Linearization of this equation yields

$$\frac{\partial Z}{\partial X}\,dX = dp/\dot{Q} - p\,d\dot{Q}/\dot{Q}^2. \tag{2}$$

With respect to the vasoactive substance the assumption is made that a constant amount per unit time is secreted or injected into the arterial blood stream. Thus the concentration of the substance decreases if the flow increases and vice versa.

$$dX = -k\,d\dot{Q}\,. \tag{3}$$

Inserting eq. 3 into eq. 2 yields the linearized input impedance

$$\frac{dp}{d\dot{Q}} = Z\left(1 - k\,\frac{\partial Z}{\partial X}\,\frac{\dot{Q}}{Z}\right) \tag{4}$$

[1] TH. KENNER and K. ONO, Experientia *27*, 528 (1971).
[2] TH. KENNER and K. ONO, Pflügers Arch. *324*, 155 (1971).
[3] TH. KENNER, Kybernetik *9* 215 (1971).

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Arterial pressure (p) and flow ($\dot{Q}$) in the femoral artery of a dog. The flow is provided by a peristaltic pump (arterial blood). The reaction of the arterial pressure to flow step increases, and decreases, are shown. Upper tracing: control. Middle tracing: during constant rate intra-arterial infusion of Acetylcholin. Lower tracing: during constant rate intraarterial infusion of Noradrenalin.