ABSTRACT

To evaluate arterial baroreceptor reflex control of total systemic vascular resistance, we studied the relation between mean arterial blood pressure (P) and mean aortic flow (Q) before and after the reflex was abrogated. In 12 dogs with a perfusion pump interposed at the vena caval–right atrial junction, Q was kept at 60, 80, 100, 120, and 140 ml/min kg\(^{-1}\) for up to 20 minutes. There was little time-dependent change in P at any of these flows. When the reflex was intact, the mean P-Q curve was only slightly convex to the pressure axis; its linearized slope was 0.55 mm Hg·min·kg\(^{-1}\)·ml and its pressure axis intercept was 44 mm Hg. After section of the sinovagal nerves, administration of hexamethonium (30 mg/kg, iv) and norepinephrine (3–5 μg/kg min\(^{-1}\), iv), or both, the slope became 0.96 mm Hg·min·kg\(^{-1}\)·ml and the pressure axis intercept was about 3 mm Hg. Similar findings were obtained in 3 closed-chest dogs in which P was servocontrolled and Q was measured. Therefore, we think that the conventional practice of calculating total peripheral resistance as P/Q and evaluating reflex control of it in terms of the changes in that value involves only a small error in the moderately sub- and supranormal flow range.

KEY WORDS carotid sinus nerve cervical vagotomy nonlinear resistance pressure axis intercept slope of pressure-flow curve total peripheral resistance flow autoregulation whole-body perfusion

The pressure difference between artery and vein (P) divided by cardiac output (Q) has been called total peripheral resistance and widely used to quantify overall vasomotor control by neural or humoral mechanisms. This calculation assumes that the P-Q curve extrapolates linearly toward the origin of the P and Q axes. Problems arise with this practice when one recalls that P-Q curves determined in some individual organs or tissues are convex to the flow axis (flow autoregulation) and that the portion of these curves in the normal P-Q range extrapolates to a positive point on the flow axis (1). If such a nonlinearity is indeed a fundamental property of the total as well as the regional vascular bed, then the effect of a given control mechanism on total systemic resistance will also have to be quantified with reference to this inherently nonlinear relation.

Several studies have addressed themselves to this problem. Folkow (2) studied the P-Q relation in kittens whose spinal cords had been destroyed; the total systemic vascular bed was then perfused under various pressures by much larger cats. The P-Q curves thus determined were mildly convex to the flow axis, indicating flow autoregulation in the whole body. Levy et al. (3) changed arterial blood pressure in closed-chest dogs and measured cardiac output before and after they severed the carotid sinus and vagal nerves. In contrast to Folkow (2), they found that after the baroreceptor reflexes had been eliminated the P-Q curve was approximately linear and extrapolated toward the origin. The latter justifies the use of total peripheral resistance in the evaluation of reflex and other controls of total systemic resistance. More recently, Granger and Guyton (4) have found that the P-Q curve in dogs that are completely deprived of their central nervous system deviates with time from the ideally linear relation, intersecting the flow axis at greater and greater values. These investigators have emphasized the importance of long-term observation of flow changes (20–30 minutes) if flow autoregulation is to be observed. Very recently, however, Liedtke et al. (5) have reported that whole body flow autoregulation becomes clearly visible in less than 5 minutes after a change in cardiac output in dogs whose carotid sinus and vagal nerves are severed, but who otherwise are intact.

This paper deals with experiments on the total...
systemic P-Q relation; these experiments differ in one aspect or another from those mentioned previously. We thought that if flow autoregulation occurred it would be seen more clearly when cardiac output was changed and fixed at abnormal levels than when arterial blood pressure was altered to the same (relative) extent. In the former condition, flow autoregulation cannot recover flow toward the control level. Instead, flow autoregulation simply changes arterial blood pressure further in the original direction of change. On the other hand, if arterial blood pressure is controlled, flow autoregulation can return flow toward the control level and thereby attenuate the primary effect of altered pressure on flow. For this reason, we varied aortic flow and held it at abnormal levels in the majority of our dogs by using a whole-body perfusion system.

To evaluate the possible distortion of the P-Q relation by the pump perfusion system, we changed arterial blood pressure in a small number of closed-chest dogs and determined the aortic flow change over a long period in a manner similar to that used in the studies mentioned previously. Both types of experiments were repeated before and after sinoaortic denervation, a massive administration of hexamethonium, or both, so that baroreceptor reflex control of the total systemic P-Q relation could be evaluated with reference to the denervated P-Q curve. In this paper, we will use the term "flow autoregulation" to mean significant deviation of data points toward the flow axis from the idealized linear relation connecting the origin and the control P-Q data. In parallel with this definition, we will refer to the term when we discuss a time-dependent change in pressure or flow under conditions of controlled flow or pressure in denervated dogs.

Methods

Two different sets of experiments were conducted. In the first series of experiments, 12 mongrel dogs (19-29 kg) were anesthetized with sodium pentobarbital (30 mg/kg, iv), and a perfusion pump was inserted between the caval veins and the right atrium so that aortic flow (cardiac output minus coronary flow) could be held at various constant levels. In the second series of experiments, a flow transducer was chronically implanted around the ascending aorta in 3 dogs, and pressure was varied while aortic flow was recorded. In both groups of dogs, the left and right carotid sinus areas were exposed, and loose ligatures were placed around the nervous and connective tissues between the external and internal carotid arteries so that the sinus nerves could be ligated and functionally destroyed when desired. At this time, the vagi were sectioned at the level of the tracheal cannula.

Surgical Procedures

In the first series of experiments, a right thoracotomy was performed at the fifth intercostal space under positive-pressure ventilation with a mixture of 95% O2-5% CO2. Arterial blood samples were frequently withdrawn for blood gas analysis, and the ventilation was adjusted to maintain the partial pressure of oxygen (P9O2) and the partial pressure of carbon dioxide (PCO2) within their normal ranges. The right atrial appendage was cannulated first and connected to the outflow side of a perfusion pump (Sarns model 5M6002) primed with a mixture of equal amounts of isotonic saline and 6% dextran solution (Macrodex). The superior vena cava was then cannulated and connected to the inflow side of the perfusion pump. Perfusion was immediately started with an initial flow of about 40 ml/min kg^-1. The inferior vena cava was cannulated next. Pump flow was increased to accommodate the additional venous return. Ligation of the azygos vein completed the surgery. Cautery and complete ligation of cut wounds were used to minimize blood loss. Constancy of the perfusion pump's flow was continuously monitored by an electromagnetic flowmeter system (Statham K2000) and an extracorporeal flow transducer. The volume flow rate through the perfusion pump was preliminarily calibrated using a graduated cylinder and a stopwatch. Based on this calibration, the pump flow rate in the control condition was set at 100 ml/min kg^-1 for all dogs in this series.

Central mean arterial and venous pressures were measured through catheters placed in the thoracic aorta and the inferior vena cava via the right femoral artery and vein, respectively, and connected to pressure transducers (Statham P23AC and P23BB). The zero pressure reference was set at the junction of the inferior vena cava and the right heart under direct inspection. Catheters were also placed in the left femoral artery and vein; blood samples for gas analysis were periodically drawn from the arterial catheter and norepinephrine was infused via the venous catheter. Artificial respiration was adjusted to maintain blood gases within their normal range. Central venous pressure was maintained at a level near zero by adjusting the level of the venous reservoir. Therefore, arterial blood pressure was regarded as the driving perfusion pressure.

In the second group of three mongrel dogs (24-28 kg), we implanted an ascending aortic flow probe (Statham Q series) 7-10 days before the experiment. On the day of the experiment, the dogs were anesthetized with sodium pentobarbital (20 mg/kg, iv), and their central arterial and venous pressures, aortic flow, and blood gases were monitored as they were in the first series of experiments. To change and to maintain arterial blood pressure at the desired levels, we used basically the same method as did Granger and Guyton (4). A 2-liter reservoir was half filled with a mixture of equal amounts of 6% dextran solution and isotonic saline and connected with the dog’s femoral artery. The top of this reservoir had a servocontrolled valve that allowed compressed air to flow into the reservoir or to leak out from it, depending on whether the arterial blood pressure was below or above a desired level. To minimize the effect of alteration of viscosity consequent to a massive fluid infusion when the P-Q relation at the high pressure range was being studied, we...
initially set the desired pressure at 60 mm Hg to mix the fluid in the reservoir with the dog's blood prior to the beginning of the experiments. With this system, mean arterial blood pressure could be set and maintained within ± 2 mm Hg of the desired level. Aortic flow was continuously recorded by an electromagnetic flowmeter (Statham K2000) and calibrated in vivo at the end of the experiment by inserting a pump perfusion system as described in the first series of experiments. We primed the reservoir with dextran solution in isotonic saline to avoid the consequences of reactions produced by using blood from donor dogs.

**EXPERIMENTAL PROTOCOL**

In the first series of experiments, the relation between aortic flow and mean arterial blood pressure was first established before the moderator reflexes were abrogated (intact condition). Aortic flow was changed in steps from the control level to 80, 60, 40, 120, and 140 ml/min kg⁻¹, always allowing for a full recovery of pressure toward the control level between steps. In the intact condition, aortic flow was maintained at each level for a period of 5-15 minutes, which was followed by another period of 5-10 minutes for pressure recovery. In eight dogs subjected to this study, the vagi were sectioned and the carotid sinus nerves destroyed by tying the ligature. Bilateral occlusion of the common carotid arteries was used to confirm the completeness of the denervation procedure. When mean arterial blood pressure had stabilized at a new level, step changes in aortic flow were carried out as they had been in the intact condition. In seven dogs, autonomic denervation was accomplished by administering a large amount of hexamethonium chloride (30 mg/kg, iv). As a result, arterial blood pressure dropped to 40-60 mm Hg. It was then reelevated to its normal level between 100-150 mm Hg by infusing norepinephrine (3-5 μg/kg min⁻¹). Mean arterial blood pressure was allowed to stabilize, and the preparation was tested for any residual reflex response by bilateral occlusion of the common carotid arteries. Aortic flow was then changed as it had been in the intact condition.

In the second series of experiments, the pressure-flow relation was studied by lowering and raising mean central arterial pressure in steps separated by control periods; the resulting changes in ascending aortic flow were observed. Pressure was changed by adjusting the reference voltage to the servomechanism which caused blood to flow either into or out of the reservoir bottle. In these experiments, aortic flow was monitored for up to 40 minutes after a step increase or decrease in pressure and then for a similar period after the recovery of pressure toward control levels. As in the first series of experiments, the dogs were studied with their nerves intact first, sinovagal denervation followed, and finally ganglionic blockade and norepinephrine infusion were carried out.

**Results**

**PRESSURE RESPONSE TO STEP CHANGES IN AORTIC FLOW**

The pressure responses determined in a typical experiment of this series are shown in Figure 1. Aortic flow was decreased from the control level of 100 ml/min kg⁻¹ to 80, 60, and 40 ml/min kg⁻¹, first with the nerves intact (top) and then after administration of hexamethonium (middle). Within 2 minutes after these decreases in flow, mean arterial blood pressure fell from about 128 mm Hg to 118, 103, and 84 mm Hg in the intact condition and from 98 mm Hg to 80, 59, and 40 mm Hg after ganglion blockade. Note that a slight but clear recovery of pressure is visible in the denervated condition during the 15 minutes of observation. This trend is opposite to what would happen if the systemic vascular bed decreased its resistance with time in an attempt to maintain flow. We saw no clear time-dependent decreases in arterial blood pressure in this or other dogs of this series except for one case in one dog. We repeated the experiment while the dog considered in Figure 1 was ventilated with hypoxic air (10% O₂ in 90% N₂) and arterial Po₂ was lowered to about 60 mm Hg. Again, we did not observe a time-dependent decrease in arterial blood pressure (Fig. 1, bottom). Another dog in which arterial Po₂ was lowered to 50 mm Hg

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mm Hg also failed to show any clear sign of flow autoregulation.

Figure 2 illustrates the averaged time course of pressure responses to changes in aortic flow of ± 40% and ± 20% of control. The data points represent mean pressure values in percent of the control value, and the bars represent ± 1 SE. The intact data include 11 dogs, whereas the denervated data represent 8 dogs and the hexamethonium data consider 6 dogs. The mean pressure values when aortic flow was 100 ml/min kg⁻¹ were 100 ± 5 (SE) mm Hg for the intact condition, 106 ± 9 mm Hg for the denervated condition, and 98 ± 4 mm Hg for the ganglion-blocked condition. After aortic flow had been returned to the control level, arterial blood pressure recovered to or near the control level (98 ± 3% of the control pressure). When a paired t-test was applied to the meaned time-dependent changes in pressure in the denervated condition, the data between 2 and 10 minutes after the 40% decrease in aortic flow indicated a statistically significant increase of 4.5%.

The relation between arterial blood pressure and aortic flow obtained in this series of experiments is shown in Figure 3. The data points represent mean pressure responses 5 minutes after aortic flow was changed, both before and after surgical or pharmacological denervation. It is clear from the figure that the relation can be approximated reasonably well by rectilinear curves, although there is a slight convexity toward the pressure axis for each set of data. Since the percent pressure-flow data plotted from individual dogs could also be approximated by a linear relation, we visually fitted straight lines to these plots and determined the slope and the pressure intercept of these fitted lines. These values and their means ± SE are listed in Table 1. The lines in Figure 3 were visually fitted to the mean data. The broken line (intact condition) has a slope of 0.60 and a pressure intercept of 40%. The solid line (surgically and pharmacologically denervated condition) has a slope of 0.92 and a pressure intercept of 10%. Independent of this analysis, the slope and the pressure intercept were obtained by applying linear regression analysis to the pooled data. The values obtained by this procedure were 0.58 and 42% for the intact condition, 0.89 and 11% for the sinovagal denervated condition, and 0.92 and 8% for the pharmacologically denervated condition.
dition. Since there was no significant difference between the two denervated subsets, a single set of mean slope and intercept of 0.9 and 10%, respectively, was calculated for the pooled denervated condition. The results of regression analysis are in close agreement with the rectilinear lines (Fig. 3) visually fitted with the mean pressure-flow data.

FLOW RESPONSE TO STEP CHANGES IN ARTERIAL BLOOD PRESSURE

The flow responses seen in one of the three dogs in this series of experiments are shown in Figure 4; data collected under intact condition (top), after sinovagal denervation (middle), and after administration of hexamethonium (bottom) are shown. In each section, the left side represents the 30-minute time course of flow after a 20% step decrease in arterial blood pressure by the servomechanism, and the right side represents the time course after a 40% reduction in pressure. Compared with the first series of experiments, flow appeared to decrease to the steady-state level and recover toward control much more slowly. The recovery also appeared to be less complete, although an exact comparison is difficult because of the smaller number of dogs studied in this series. Once again, there was no significant increase in flow with time.

We plotted pressure-flow data from the three dogs in the same way that we did for the first series of experiments and fitted a rectilinear line for the intact and the denervated data; mean values of these individually estimated slopes and intercepts were calculated. Linear regression analysis applied to the intact data gave a slope of 0.6 and a positive pressure intercept of 40%. After surgical and pharmacological denervation, the slope increased to 1.0 and the pressure intercept decreased to 0.0%. The control arterial blood pressure was 118 mm Hg in the intact condition, 110 mm Hg after surgical denervation, and 100 mm Hg after pharmacological denervation.

Although the reliability of the data from the second series of experiments is severely limited by the small number of samples, the data suggest the same trend as that seen in the first series of experiments. In the intact condition, the barore-

<table>
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<th>$\Delta P/\Delta Q$ (mm Hg · min · kg$^{-1}$) ml</th>
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*TABLE 1*

*Slope (ΔP/ΔQ) and Intercept (Po) of P-Q Curves Linearly Fitted to Data from Individual Dogs in the First Series of Experiments.*
TOTAL RESISTANCE AND THE BAROREFLEX

cceptor reflex alters total systemic resistance so as to maintain arterial blood pressure within a small range, whereas, after denervation, the resistance remains almost constant, regardless of increases or decreases in arterial blood pressure, over a period of up to 40 minutes.

Discussion

For a quantitative description of baroreceptor reflex control of total systemic resistance, information is needed about how total systemic resistance responds to sub- or supranormal flows or pressures in the absence of the reflex control. The present study attempted to determine this information rather than to explore the mechanism of flow autoregulation.

Levy et al. (3) conducted an experiment quite similar to the second series of experiments in the present study. Unfortunately, they reported the percent values of total peripheral resistance (TPR) as the main body of data, and we cannot reconstruct from their TPR values the original pressure-flow curves. However, an example of the pressure-flow relations that they presented in Figure 2 of their paper strongly resembles our curves in Figure 3. Namely, without reflex control, the pressure-flow curve extrapolates toward the origin, whereas, with the reflex intact, the slope of the nonlinear curve is less steep and extends toward a positive pressure intercept. Since the authors stated that other dogs showed a similar relation, we think that the present data, obtained mostly with the use of a pump perfusion system, are in good agreement with the results of Levy et al. (3) obtained without a perfusion pump.

To eliminate not only the surgical traumas to the animal but also other mechanisms possibly triggered by blood volume changes, Liedtke et al. (5) depressed or enhanced performance of the cardiac pump by a temporary underperfusion or an infusion of calcium ions into the coronary bed. As we did in this study, they fitted a rectilinear curve to the individual pressure-flow data and reported the slopes and flow axis intercepts of these linearized curves. Again, before sectioning the sinus nerves and vagi, they found relatively shallow slopes and large negative intercepts on the flow axis (which means large positive intercepts on the pressure axis as in the present study). After the sinoaortic denervation, most of the fitted lines intersected the flow axis at positive points very close to the origin. If they had eliminated one dog (out of eight) which showed an exceptionally large value for the flow intercept, the mean intercept value would have been even closer to zero. And yet, they concluded that total body autoregulation occurred following ablation of the carotid sinus and the aortic arch baroreceptors. This conclusion is based on the facts that all of the values for the flow axis intercept converted from negative to positive and that their mean value (0.9 liters) was significantly different from zero. Although the logistics of their conclusion may be valid, the small flow axis intercept makes us feel that their findings are substantially the same as those of Levy et al. (3) and the present study. At most, the degree of flow autoregulation present in their P-Q relation data after baroreceptor denervation is extremely weak compared with that which Granger and Guyton (4) have reported.

Granger and Guyton (4) decapitated their dogs, a procedure that removes not only the brain but also neuroendocrines such as antidiuretic hormone, adrenocorticotropic hormone, etc. Their preparation, therefore, had a smaller number of control mechanisms for arterial blood pressure regulation than did most of the other investigators’ dogs. In their preparation, they observed a strong flow autoregulation which developed over 20–30 minutes after a change in arterial blood pressure. According to their calculation, the flow autoregulation had an overall open-loop gain of 3.3. There is reason to believe that this aforementioned open-loop gain of the total systemic flow autoregulation is considerably underestimated. Cowley et al. (6) have demonstrated in the same preparation that the renin-angiotensin system works to restore a fall in renal arterial blood pressure with an overall feedback gain of 2, which is comparable to that of the carotid sinus baroreceptor reflex. We could not find in the present experiments any sign of such a high-gain feedback control for maintenance of flow. Instead, we observed a statistically significant pressure recovery after a 40% reduction in aortic flow in the denervated condition (Fig. 2). However, the degree of recovery was only 4.5%, and we do not consider this to be of great importance.

Our failure to see a clear indication of flow autoregulation is not surprising at all considering a more recent report by Shepherd et al. (7) from Guyton’s laboratory. In this latest study, the authors made a more detailed analysis of the conditions under which the total systemic resistance exhibits flow-autoregulatory behavior in response to underperfusion. As a result, they found that, unless the experimental animal’s tissues are rendered severely hypoxic by infusing vasoconstrictor (epinephrine) to lower control cardiac output or by ventilating with an hypoxic gas mixture, no tangible flow-autoregulatory response can be elicited in response to about a 50% decrease in arterial blood pressure.
pressure. As mentioned in Methods; we ventilated our dogs to ensure normal arterial Po₂. Therefore, the tissues of these dogs could still obtain enough oxygen from the decreased flow by increasing O₂ extraction, according to the hypothesis advanced by Shepherd et al. (7). Although we rendered two dogs hypoxic (Po₂ at 50 and 60 mm Hg) before reducing aortic flow, this degree of hypoxia was not enough to provoke flow autoregulation in the systemic vascular bed as a whole.

To simplify the data presentation, we approximated the pressure-flow relation by a rectilinear curve. As mentioned earlier, there is in fact a slightly curvilinear relation, convex toward the pressure axis, between the pressure and the flow data obtained in the intact condition (Fig. 3). This nonlinear P-Q relation is to be expected when the baroreceptor reflex control of total systemic resistance is intact. Assume that in the arterial blood pressure range from 75 to 125 mm Hg, the transfer gain of the sinoaortic reflex on the resistance, Gr, is −0.01 peripheral resistance units (PRU) (mm Hg-min·kg/ml) per 1-mm Hg change in receptor pressure. This assumption is a reasonable one in reference to our previous studies on the open-loop gain of carotid sinus reflex control (8-10). Also assuming that control arterial blood pressure (Pc) is 100 mm Hg, control cardiac output by Q, and control total peripheral resistance (TPRc) = 1.00 PRU, we can calculate the arterial blood pressure response to changes of aortic flow to 60, 80, 120, and 140% of control. The formula for this calculation is described in the Appendix. This theoretical calculation and the experimental data for the baroreceptor reflex-intact condition are plotted in Figure 5. The two sets of values agree fairly well in the subphysiological P-Q range but less well in the supracontrol range. The aim of this comparison is to show that the nonlinear P-Q relation is probably due in major part to the baroreceptor reflex.

In summary, the present study indicates that, in a range from 60 to 140% of the normal pressure and flow, total systemic vascular resistance remains approximately constant, unless the sinoaortic baroreceptor reflexes intervene. In the normal situation, the reflexes increase or decrease the resistance as pressure decreases or increases. The study also indicates that it is difficult to detect significant flow-autoregulatory behavior of total systemic resistance within a period of up to 30 minutes. Although we still cannot say why this lack of autoregulation is so despite the well-known flow autoregulation in many systemic vascular beds, these results suggest that evaluating reflex control of total systemic resistance in terms of conventional total peripheral resistance is an acceptable practice after all.

Appendix

Assume that within the ranges of P and Q of interest, the arterial baroreceptor reflex has a constant transfer gain, G, with which it translates a change in arterial blood pressure from control (ΔP) into a directionally opposite change in total peripheral resistance from control (ΔTPR): namely, ΔTPR = G × ΔP. This assumed mechanism is schematically shown in Figure 6. The control arterial blood pressure is represented by Pc, the control resistance by TPRc, and the control cardiac output by Q, in this diagram. Thus, when Q = Qc and TPR = TPRc, P = Qc × TPRc = Pc. But if Q is varied from Qc, it will be seen from the diagram that

\[ P = Qc(TPRc + ΔTPRc) = Qc(ΔTPRc + G(Pc - P)). \]

Rearranging this equation yields

\[ (1 + G \cdot Qc)P = Qc(TPRc + G \cdot Pc), \]

\[ P = \frac{TPRc + G \cdot Pc}{1/Qc + G}. \]

On the right side of Eq. 1, the numerator and G in the denominator are constant. Therefore, P = 0 when Q = 0; with increases in Q, P increases nonlinearly towards an asymptote which is equal to (TPRc + G • Pc)/G. The theoretical P values in the range of Q from 0.6 to 1.4 Qc were calculated from Eq. 1 using a previously obtained value for G. These values were compared with the present experimental data on the P-Q relation in Figure 5.
**References**


2. Folkow B: Study of the factors influencing the tone of denervated blood vessels perfused at various pressure.


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**FIGURE 6**

Block diagram of baroreceptor reflex control of total peripheral resistance (TPR) in the first series of experiments. See the text for definition of other abbreviations.
Static pressure-flow relation in the total systemic vascular bed of the dog and its modification by the baroreceptor reflex.
K Sagawa and A Eisner

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