Starling Resistor Versus Compliance
Which Explains the Zero-Flow Pressure of a Dynamic Arterial Pressure-Flow Relation?

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Arterial pressure at zero flow (Pz=0) that is higher than venous pressure (Pv) in dynamic pressure-flow relations has been explained by the presence of an arteriolar Starling resistor (SR) mechanism (i.e., vascular waterfall) or the discharge of vascular capacitance. To determine which was predominant, I studied in vivo hind limbs of 18 anesthetized dogs in which femoral arteries were cannulated with in-line electromagnetic flow probes to measure inflow (Qin), Pv was controlled, and collateral flow was eliminated with a tourniquet. Pz=0 was obtained by turning flow to zero. Three tests were applied: 1) Pv was raised in steps with either constant Qin or constant arterial pressure (Pa) to determine the pressure at which upstream vascular characteristics were affected by a change in Pv, 2) the time to reach Pz=0 was varied to determine compliance effects, and 3) an equation was developed to determine if experimentally derived parameters could explain Pz=0 without invoking an SR. With constant Qin and a Pz=0 of 56.9±11.7 mm Hg (time to Pz=0, 3 seconds), Pv could be raised by 9.6±6.2 to 16.3±6.0 mm Hg before Pa increased, and with constant Pa, Pv could be raised by 6.8±7.3 to 14.0±8.0 mm Hg before Qin decreased. With increasing times to reach Pz=0, Pz=0 initially dropped precipitously, but then decreased by only a small amount over the next 5–10 seconds even though arterial pressure was much above Pv. This could be explained by an SR mechanism with a critical pressure of 42.3±11.4 mm Hg and an arterial compliance of 0.0104±0.0023 ml/mm Hg–1 (n=6). There was no value for the compliance that described the results when the arterial outflow pressure was Pv. Thus, this study supports the hypothesis that an SR mechanism is present in the vascular system. It is most likely precapillary, and in the resting limb, it has a value of 40–50 mm Hg. However, Pz=0 in dynamic pressure-flow studies of less than 4 seconds is also greatly influenced by capacitance effects and the initial Pa. (Circulation Research 1990;67:209–220)

If vascular resistance is proportional to the pressure difference between an artery and vein and is inversely proportional to the flow in that region, then arterial pressure (Pa) should equal venous pressure (Pv) when the flow into the region (Qin) is zero. However, it has been shown repeatedly that Pa is greater than Pv when Qin=0.1–7 The potential significance of this for the measurement of vascular resistance received increased attention after Bellamy’s8 analysis of canine coronary diastolic pressure-flow relations in which he found that the pressure at Qin=0 (i.e., zero-flow intercept of the pressure-flow relation, which will be called Pz=0)

was 30–50 mm Hg when the Pv was only 5–10 mm Hg. He proposed that Pz=0 was due to a vascular waterfall, or Starling resistor mechanism, as described by Permutt and Riley9 at the level of the arterioles. Consistent with this hypothesis, factors such as an increase in heart rate or pharmacological interventions that increase coronary flow and should produce arteriolar dilation decreased Pz=0.8 He thus reasoned that coronary flow could be regulated by changes in vessel diameter, that is, changes in resistance or changes in the arteriolar tone that cause changes in Pz=0. Furthermore, according to this hypothesis, in a well-autoregulated organ such as the heart, Pz=0 could be measured only in dynamic studies, because tone would change with steady-state decreases in pressure and Pz=0 would be underestimated. In support of his observations, Pz=0 values much higher than Pv have also been found with dynamic pressure-flow studies in the brain,10,11 kidney,12 and hind limb,13,14

A potential fallacy in this reasoning was soon identified by Spaan15 and Eng et al,16 who proposed

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that \( P_z=0 \) in dynamic studies is due to discharge of vascular capacitance at or downstream from the point of the flow and pressure measurements. Thus, resistance should still be calculated from the difference between \( P_a \) and \( P_v \), but only during steady-state conditions to avoid transients produced by flow from compliant regions as the pressure falls. Attempts were made to eliminate the compliance flow by various techniques, including examination of decreasing and increasing pressures and analysis of impedance, but these techniques do not rule out pressure-dependent changes in resistance that may also be important. In addition, the fact that venous flow continues when inflow is zero does not account for the capacitance, because this flow could be distal to the Starling resistor. Considering the importance of the measurement of resistance in hemodynamic studies and the important implications of the alternative explanations of \( P_z=0 \) (i.e., a Starling resistor versus compliance effect), this controversy needs to be resolved. I therefore examined dynamic arterial pressure-flow relations in in situ isolated dog hind limbs in which a dynamic \( P_z=0 \) of greater than 60 mm Hg had previously been found.

Three tests were applied. First, \( P_v \) was raised in steps to determine if changes in \( P_v \) below \( P_z=0 \) would affect \( Q_m \) or \( P_a \). If the \( P_z=0 \) was due to a Starling resistor mechanism or critical pressure, then elevating \( P_v \) should have no effect until the critical pressure is overcome. Second, the time to reach zero flow was varied from 1 to 10 seconds; if \( P_z=0 \) was due to arteriolar tone and a Starling resistor mechanism, then there should be no variation in \( P_z=0 \) with times to zero flow that are short, because autoregulatory adjustments of arterial tone are believed to take approximately 4 seconds to occur. With times greater than 4 seconds, \( P_z=0 \) should decrease. Alternatively, if \( P_z=0 \) was due to pressure in a downstream compliant region, then there should be a progressive fall in pressure with increasing times to \( P_z=0 \). Third, a mathematical model was constructed to determine if a reasonable estimate of vascular compliance could be found to account for the \( P_z=0 \) observed in the second test with variable times to zero flow.

### Materials and Methods

#### Surgical Preparation

Eighteen mongrel dogs weighing 15–22 kg were studied. They were anesthetized with 25 mg/kg sodium pentobarbital, which was supplemented with 0.5–1 mg/hr, as necessary. The animals were intubated and ventilated with a volume respirator (tidal volume, 12–15 ml) (Harvard Apparatus, South Natick, Mass.) throughout the experiment, and \( O_2 \) was supplemented as needed. Animals were included only if their hematocrit was above 35.

The right femoral artery was isolated and cannulated to monitor \( P_a \) and to withdraw blood for blood-gas analysis; the femoral vein was cannulated for the administration of medication, and 0.9% saline was slowly infused to account for volume losses during the experiment. The left femoral artery was isolated in the femoral triangle. It was ligated, and a metal cannula with a side-port for pressure measurement (Pa) was inserted in the distal end of the vessel beyond the ligation. The cannula was connected to an electromagnetic flow probe (Carolina Biological Supply Co., Burlington, N.C.) that was attached to a Y connector. One arm of the Y was connected to a cannula in the proximal segment of the femoral artery above the ligature, and the other was connected to a line that was connected to a pump that withdrew blood from the left carotid artery.

A 16-gauge spinal needle was used to pass surgical wires through the thigh and under the femoral artery, vein, and nerve. These were tied securely to eliminate collateral flow to the leg. Finally, \( Q_m \) was stopped temporarily, and the femoral vein was ligated in the middle of the femoral triangle. The distal end was cannulated, and a side-port from the catheter was used to measure pressure. In some animals, another flow probe was placed on the cannula. The venous outflow then passed through collapsible tubing (Penrose Drain, American Hospital Supply, Ill.), which could be raised or lowered to control the \( P_v \); the blood flow was then returned to the proximal femoral vein.

#### Measurements

Pressures were measured with Transect transducers (American Edwards Laboratories, Santa Ana, Calif.) connected to preamplifiers and an eight-channel recorder (models 8805A and 7418A, Hewlett-Packard Co., Palo Alto, Calif.). The flow signal and arterial pressure were recorded on a four-channel tape recorder (Teac R-60, P.I.D. Institute, Toronto, Canada) for later analysis on an IBM-PC equipped with an analog-to-digital converter and programmed to calculate the pressure-flow relation.

#### Procedures

**Dynamic pressure-flow measurements.** In eight animals, the hind limb was perfused with blood from the proximal femoral artery so that the “natural” flow requirement of the limb could be determined. The proximal line was then clamped, and the pump was adjusted to give the same mean flow as the natural flow. Pump flow was then manually turned to zero at a constant rate over approximately 3 seconds and kept at zero for 6 seconds. The flow was then returned to control for approximately 2 seconds and then turned to zero again to test the pressure-flow relation with reactive hyperemia (Figure 1). Four or five measurements were obtained for each dog. Next, muscle twitches were produced with supramaximal voltages, 5-Hz stimulations, and 15-msec duration. When flow had stabilized, the same procedure was repeated with a decrease in flow to zero, arrest of flow for 6 seconds, and a second “reactive” run.

**Variable venous pressures.** These studies were performed with either constant \( Q_m \) or constant \( P_a \) in 10
dogs. $Q_{in}$ was provided by the pump. First, three measurements of $P_{z}=0$ were obtained by turning the flow to zero over 3 seconds and back to control. The Starling resistor on the venous outflow was then raised in steps, and changes in $Pa$ were recorded. In some of these studies, $P_{z}=0$ was also recorded by turning the flow to zero at different levels of $P_{v}$.

For constant $P_{a}$, $P_{v}$ was altered as above, and perfusion was provided from the native proximal femoral artery, which was not affected by raising $P_{v}$ of the leg and therefore represents constant-pressure studies. In these studies, changes in $Q_{in}$ were recorded. Both constant-flow ($n=5$) and constant-pressure ($n=6$) studies with changes in venous pressure were also performed after the injection of 10 mg phentolamine into the femoral artery.

**Variable time to zero flow.** Dynamic pressure-flow studies were obtained by turning flow to zero over 1–10 seconds and then back to control flow at the same rate in six dogs. Seven to 15 measurements were obtained for each animal, and the values of $P_{z}=0$ were plotted against time to zero flow.

**Analysis of Dynamic Pressure-Flow Relations**

The data from dynamic pressure-flow studies were digitized on an IBM-PC that sampled the signal at 50 Hz. The $Q_{in}$ was plotted against $P_{a}$, and a linear regression equation was calculated. There was a small initial curvilinear phase and then a linear relation. The program gave the slope of the linear phase and $P_{z}=0$, which is the $x$-intercept of the equation (see Figure 1). As can be seen in the analog signal, pressure continued to fall when inflow was zero, but the pressure-flow line included only the points until the time when inflow reached zero.

**Statistics**

Data are presented as mean±SD. When repeated measurements were obtained, an analysis of variance for repeated measurements was used to first determine if there was a significant variation in the population; when significant differences were found between groups, they were analyzed with a Newman–Keuls test. Relations between linear variables were analyzed by linear regression analysis.

**Results**

**Dynamic Pressure-Flow Relations**

For the eight dogs in which reactive hyperemia and contractions were studied, the initial $P_{a}$ at rest was $131±21.6$ mm Hg, and with 5-Hz stimulation it was $123.1±17.3$ mm Hg. The control flow was $139.8±48.6$ ml/min, and with 5-Hz stimulation it rose to $250.3±43.5$ ml/min ($p<0.01$). The control $P_{v}$ was $3.9±1.4$ mm Hg, and with 5-Hz stimulation it rose to $4.9±2.0$ mm Hg. When $Q_{in}$ in the resting hind limb was reduced to zero over 2–3 seconds, the resulting pressure-flow line was most often linear, although the relation was sometimes curvilinear with a convexity to the pressure axis at low flows. An example is shown in Figure 1, and the mean data are presented in Figure 2. The average $P_{z}=0$ was $71±16$ mm Hg, and the mean correlation coefficient ($r$) was $0.96±0.03$. It is important to note that $P_{a}$ continued to fall after $P_{z}=0$, and although it was not systematically studied, it was clear from later studies that venous flow continues when $Q_{in}$ is zero.

When $Q_{in}$ was returned to the control level after 6 seconds of occlusion and the maneuver was repeated, $P_{z}=0$ decreased to $64±16$ mm Hg. With hind-limb contractions, $P_{z}=0$ decreased to $50±18$ mm Hg and to $40±19$ mm Hg in the reactive run after 6 seconds.

![Figure 1. Example of dynamic pressure-flow run. Upper panel: The analog signal. The flow was reduced to zero over 4 seconds (run 1), occluded for 6 seconds, restored momentarily, and then decreased again (reactive run). Lower panel: The digitized pressure-flow plots for run 1 and reactive run. Note that the relations are linear. (R-2 is the square of the correlation coefficient). The slope is steeper and the x-intercept (PO) is lower during the reactive run. Pressure continues to fall while inflow remains at 0.](image-url)
of vascular occlusion. The data from eight animals are summarized in Figure 2. The slope of the incremental pressure-flow lines became progressively steeper, and Pz=0 became lower with the “reactive” run, muscular contractions, and the reactive run plus contractions.

In a manner similar to the approach of Aversano et al.,20 pressure-flow relations were also obtained by linearly decreasing and increasing flow to try to remove capacitance effects, because Aversano et al. proposed that a “capacitance-free” pressure-flow line lies between the decreasing and increasing

Figure 2. Average pressure-flow relations for eight dogs (35 runs) obtained as in Figure 1 during control run, reactive hyperemia, muscle contractions (5 Hz), and muscle contractions plus reactive hyperemia. With reactive hyperemia and muscle contractions, the zero-flow intercept of the pressure-flow relation decreased and decreased further during the reactive run with muscle contractions.

Figure 3. Digitized pressure and flow signals and pressure-flow plot for increasing and decreasing flows. The upper plots show a decrease followed by an increase in flow to double the control. The plots show an increase followed by a decrease in flow. The position of the second up phase is very dependent on the duration of arrested flow.
phases of the pressure-flow relation. In addition, the pressure was observed as the flow was increased to double that of the control flow. An example with “down” first, then “up” is shown in Figure 3 (left panel), and up first, then down is shown in Figure 3 (right panel). The up phase after a down phase of the pressure-flow relation was shifted to the left but was linear so that Pa was lower than the control Pa when Qm returned to the control level. As can be seen in the example, the shift was dependent on the time that Qm was zero (i.e., greater in the lower example than in the upper). With the up first, there was a small shift to the left during the down phase and a larger shift to the left with the next up phase.

Changes in Venous Pressure

Constant flow. Figures 4A and 4B are plots of Pa versus Pm for 10 dogs in which Qm was constant and Pm was elevated in steps. They are separated simply for clarity. In some dogs (e.g., 3, 5, and 7), Pm could be varied to greater than 20 mm Hg before Pa changed, whereas in other dogs, small changes in Pm produced increases in Pa. Mean results are shown in Figure 5. The average change in Pm before a change in Pa was 9.6±6.2 mm Hg; Pm=0 for these animals was 56.9±11.7 mm Hg (based on a 4-second decline in Qm).

In five animals treated with phentolamine, the change in Pa for a change in Pm was more consistent (Figure 6), and in only one animal (dog 6) could Pm be raised by more than a few millimeters of mercury without an increase in Pa; the mean was 2.6±4.3 mm Hg. In these five animals, Pm=0 was 35.6±9.7 mm Hg with phentolamine and 54.1±26.9 mm Hg without.

Constant pressure. Qm with changes in Pm is shown in Figure 7A. In most animals, Pm could be raised by a small amount before Qm decreased. The mean change (Figure 5) in Pm before a change in Qm was 6.8±7.3 mm Hg with a range of 0–20 mm Hg; the mean Pm at the change was 14.0±8.1 mm Hg. After treatment with phentolamine (Figure 7B, n=6), the change in Pm before a decrease in Qm was 2.2±3.9 mm Hg.

Pm=0 increased when Pm was increased. An example is shown in Figure 8. In four dogs, with an average

Figure 4. Plots of arterial pressure vs. venous pressure for 10 dogs in which inflow was constant and venous pressure was raised without. Panel A: Data for dogs 1, 2, 3, 4, and 6. Panel B: Data for dogs 5, 7, 8, 9, and 10. In some animals (e.g., dogs 3, 5, and 6), venous pressure could be increased without much change in arterial pressure, but in most, changes in venous pressure changed arterial pressure.

Figure 5. A histogram of the average zero-flow intercept of the pressure-flow relation (Pm=0) and venous pressure at which arterial pressure increased with constant flow or inflow decreased with constant arterial pressure. The black bars represent the average starting venous pressure for each condition. The bar marked Pm=0 indicates the average Pm=0 in each animal. The “constant flow” bar indicates the pressure to which venous pressure could be raised without a change in arterial pressure when flow was constant. The “constant pressure” bar indicates the pressure to which venous pressure could be raised without a change in inflow pressure. Data are mean±SD.
increase in $P_v$ of $28.7\pm4.5$ mm Hg, $P_z=0$ increased by $17.6\pm10.1$ mm Hg. For each animal, the slope of the pressure-flow relation decreased, indicating an increase in resistance. In three animals, PV was raised until $Q_{in}$ stopped. In each case, $Q_{in}$ became zero when $P_v=P_a$ even though the $P_z=0$ increased with increasing $P_v$.

**Variable Time to Zero Flow**

The effects of varying the time to $P_z=0$ flow are shown for six animals in Figure 9. There was an initial large fall in $P_z=0$ with increasing times to zero flow and then very little change between 5 and 10 seconds.

The initial $Q_{in}$, $P_a$, and $P_v$ for each animal were used to calculate the predicted compliance with both one-compartment and two-compartment models. The single-compartment model included a resistance, with compliance and resistance in series (Figure 9A). The decrease in $Q_{in}$ was linear as per the protocol. The solution of this equation (see "Appendix") gave

$$ (P_z=0) = P_b - \beta R_{out}^{-2} C (1 - e^{(Q_{in}/\beta R_{out} C)}) $$

(1)

where $\beta$ is the rate of change of inflow, $R_{out}$ is the outflow resistance, $C$ is the capacitance, $P_b$ is the back pressure (i.e., downstream pressure), and $Q_{in0}$ is the initial flow. The experimentally obtained values of $Q_{in0}$, $P_z=0$, $P_v$, and $\beta$ could then be used to calculate the compliance, assuming different propor-

**FIGURE 6.** Arterial pressure vs. venous pressure for five dogs treated with phentolamine.

**FIGURE 7.** Panel A: Plots of arterial flow vs. venous pressure for 10 dogs in which arterial pressure was constant. In some animals (e.g., dogs 2, 8, and 9), venous pressure could be raised by more than 10 mm Hg before the flow changed but this pressure was still much below the zero-flow intercept of the pressure-flow relation (see Figure 5). Panel B: Plots of arterial flow vs. venous pressure for six dogs treated with phentolamine.

**FIGURE 8.** Example of pressure-flow relation at venous pressure ($P_v$) of 7 mm Hg and 34 mm Hg. Both down and up phases are shown for $P_v$ of 7 mm Hg. The pressure-flow shifted rightward with the increase in $P_v$. 

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*Note: The diagrams and graphs are not transcribed here due to the nature of the content.*
tions of upstream versus downstream resistance. First, the data from the dog in Figure 10E was used to assess the model. As would be expected from a model with a single resistance and compliance when \( P_v \) was used for \( P_b \), the solution required either a high \( R_{out} \) or a large \( C \) to explain the \( P_z=0 \) of 35 mm Hg that was observed when 10 seconds was taken to reach zero flow. With \( R_{out} \) of 30% of the total resistance, the compliance had to be 4 ml · mm Hg\(^{-1} \), which required a stressed volume of 150 ml from the femoral artery of a single hind limb at the level of the inguinal ligament to the venous outflow pressure. A solution could not be found when \( R_{out} \) was less than 30% of the total resistance. With 100% of the resistance distal to the compliant region, \( C \) was estimated at 0.4 ml · mm Hg\(^{-1} \), which gave a value of 5 ml for the volume of the hind-limb vasculature. When this value of \( C \) was used to calculate \( P_z=0 \) for times to zero flow of less than 10 seconds, the curve was much steeper than observed experimentally. A two-compartment model was also tried (Figure 9B). In this model, the system begins with a small arterial resistance that empties into a region of low compliance (i.e., arteries) that then empties into an area of high resistance (i.e., arterioles) and then into an area of high compliance (i.e., venules and veins). The second compliance was varied from 0.2 to 0.8 ml ·

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**Figure 9.** Models of the circulation used for the analysis. Panel A: The initial model has a compliance between two resistances (R1 and R2). Arterial pressure (Pa) was 103 mm Hg, and venous pressure (Pv) was 7 mm Hg. The pressure in the compliant region (Cv) is Pc. Panel B: An upstream compliance (Ca) followed by another resistance, which is large, has been added (same Pa and Pv). Panel C: A Starling resistor with a collapse pressure of 42 mm Hg has been added distal to the second resistance (R2). \( P=32 \) is the pressure that is calculated at the bottom of the "waterfall." Panel D: A shunt, which is 1.5% of the total conductance, bypasses the Starling resistor.

**Figure 10.** The values of the zero-flow intercept of the pressure-flow relation (\( P_z=0 \)) with ramped decrease to zero flow of 1–10 seconds for six dogs. The observed data points are shown with boxes. The solid line shows the regression line for the measured points. The dotted line is the regression line for the values predicted by the two-compartment model. The values at short times to \( P_z=0 \) were overestimated, and those at long times were underestimated.
mm Hg·kg⁻¹·L⁻¹ and the first compliance was varied between 1/10 to 1/30 of the second compliance. The resistances were divided with R₁=5% of the total, R₂=80%, and R₃=15%. Once again, the experimental values of Qₐ and Pᵥ were used, and the series of equations describing this model were analyzed by reiteration on a PC computer with times to zero flow ranging from 1 to 10 seconds, as obtained experimentally. This model also failed to predict the experimental results (Figure 10).

Finally, the value of Pₐ in the single-compartment model (Equation 1) was set at a level just below the value of P₀ at 10 seconds. The rationale for this was that this value could represent a critical outflow pressure at the level of the arterioles (Figure 9C). The measured value of P₀ at 2 seconds was used in Equation 1 to calculate C. This C and the equation were used to predict the other P₀ values with different ramp speeds. The parameters needed to calculate the data for the six dogs in Figure 11 are shown in Table 1. For the calculations, 100% of the resistance was put distal to the compliant region, which would be arterial compliance in this case. This is justified because 1) the critical pressure is so high that the upstream compliance must be in the arteries and there is little significant resistance in large arteries and 2) the relation between P₀=0 and time to zero flow seemed to extrapolate back to arterial pressure. When the resistance was reduced to 95% of the total, there was very little difference in the results. As shown in Figure 11, this model nearly perfectly predicted P₀=0. This figure also shows the values for arterial pressure when flow was stopped for various durations. These values fell considerably below the values obtained with the ramp decrease in flow. The significance of this point will be discussed below.
Table 1. Data for Calculation of the Zero-Flow Intercept of the Pressure-Volume Relation

<table>
<thead>
<tr>
<th>Pa (mm Hg)</th>
<th>Pb (estimated) (mm Hg)</th>
<th>Q(_0)(ml·min⁻¹)</th>
<th>Pz=0 (2 seconds) (mm Hg)</th>
<th>τ (seconds)</th>
<th>Compliance (ml·mm Hg⁻¹)</th>
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<td>a</td>
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Compliance was obtained from Equation 1 and represents the arterial compliance, and the resistance is from the beginning of the leg to Pb as discussed in the text. P_a, femoral arterial pressure; P_b, outflow pressure estimated at just below the zero-flow intercept of the pressure-volume relation (Pz=0) at 10 seconds; Q(_0), initial flow; τ, time constant derived from the product of the resistance and compliance. Letters a-f refer to the dogs shown in panels a-f in Figures 10 and 11.

Discussion

The major observations in this study can be summarized as follows: 1) When flow was rapidly decreased to zero (i.e., over 1–3 seconds), the pressure at zero flow (Pz=0) was much greater than P_v. 2) Pz=0 decreased with reactive hyperemia, exercise, and phentolamine treatment. 3) Pz=0 markedly decreased when the time to zero flow was increased from 1 to 4 seconds but decreased little thereafter for up to 10 seconds. 4) Suddenly stopping the flow resulted in a much lower Pz=0 than gradually decreasing the flow. 5) Venous pressures could be increased by approximately 10 mm Hg, to 14–16 mm Hg, before there was an effect on either inflow with a constant arterial pressure or arterial pressure with a constant flow.

A number of technical factors need to be considered. Collateral flow27 must be avoided because arterial collaterals could maintain the zero-flow pressure, whereas venous collaterals would reduce the effects of venous pressure elevations. Collaterals were eliminated with a tight tourniquet around the leg; its effectiveness was checked by examining how low Pa fell after a period of arterial occlusion and also by measuring any effluent from the open pressure line with inflow occluded. Preparations were included only if there was evidence of minimal collateral flow (i.e., <5% of baseline). These tests, however, could not be repeated throughout the experiment because of their effect on the preparation, and therefore, collateral flow possibly increased during the experiment in some animals. Also, reflexes and tone were intact, so that myogenic mechanisms or venoarterial reflexes28–32 could have affected either Pa or Q(_0) during the changes in P_v. However, animals had to be studied with tone and reflexes intact because critical pressures are believed to be dependent on arteriolar tone.8,12,14,17,20,33,34

As in previous studies of dynamic pressure-flow relations, Pa was still high when arterial inflow reached zero. In the initial studies with times to zero flow of 2–3 seconds, Pz=0 was 71±16 mm Hg. This value is much higher than observed by Ehrlich et a13 in dog hind limb, but they first obstructed flow for more than 30 seconds to produce reactive hyperemia. After 6 seconds of arrested flow, Pz=0 was lower in this study and decreased further when muscle contractions were stimulated. The question remains whether this can be explained by a Starling resistor mechanism or whether it is just due to a capacitance effect.

Time to Zero Flow

With times to zero flow of 1–4 seconds, there was an exponential decrease in Pz=0 and little change in Pz=0 thereafter for up to 10 seconds. The first model used to analyze these results included a resistance, followed by a compliant region that emptied through another resistance (Figure 9). When P_v was used as the outflow pressure (P_b), the calculated compliance was much too high for what would be expected in the leg.26 On the other hand, a more reasonable estimate of compliance could be found only if most of the resistance was distal to the compliant region. This would require that the compliant region be in the arteries rather than the veins, in which case the compliance was too large for an arterial compliance. Finally, when the compliance value from the 10-second ramp was put in the equation to try to predict Pz=0 at other times to zero flow, Pz=0 was greatly overestimated at short times to zero flow and underestimated at long times to zero flow. Most importantly, there was no value of compliance that would have predicted a plateau of Pz=0 with increasing times to zero flow, as was observed (Figures 10 and 11). The model was not improved by putting a second compliance in series with the first (Figure 10). The data, however, were almost perfectly described by using a P_b that was much higher than P_v and very close to the Pz=0 at 10 seconds, as would occur with a Starling resistor mechanism. In this case, the slope of the pressure-flow line is determined by the resistance between Pa and this outflow pressure that I will call the critical pressure or P_b to distinguish it from Pz=0, which is the observed pressure at zero flow. Distal to this P_b, or Starling resistor, are the capillaries, venous capacitance, and venous resistance.
Importantly, as long as capillary pressure is less than \( P_b \), venous resistance will not contribute to the resistance to inflow, and flow will simply be determined by \( P_a \) minus \( P_b \) divided by the arterial resistance.

A problem with this analysis seems to arise when the experiments in which inflow was abruptly stopped are examined, because \( P_z=0 \) fell to levels much below the \( P_b \) determined by the ramp decreases in flow of up to 10 seconds (Figure 11). The Starling resistor hypothesis predicts that even with a sudden arrest in flow, the \( P_a \) should fall only to \( P_b \). This observation, however, can be explained easily by the presence of arterial collaterals that bypass \( P_b \) and need a conductance of only 1.5% of the total. Therefore, when \( P_a \) falls to the level of \( P_b \), flow can continue through the collaterals, but because of the low conductance, the pressure drops very slowly. This value of conductance can be used to predict that, as observed, the \( P_z=0 \) at 30 seconds is still greater than \( P_v \). Of note, the conductance for determining the fall in \( P_a \) is the conductance through the collaterals, which is only 1.5% of the total. The data from the studies of variable times to zero flow can thus be explained very well by a Starling resistor mechanism with the coexistence of a small amount of collateral blood flow. These results, however, also show that the arterial capacitance has a significant effect on the \( P_z=0 \) with short times to zero flow (i.e., <4 seconds).

Changes in Venous Pressure

Although the data on variable times to zero flow can be explained well by a Starling resistor mechanism, the results from changes in \( P_v \) with a constant inflow or constant \( P_a \) might at first seem to contradict the hypothesis because \( P_v \) could be increased by approximately only 10 mm Hg, to 14–16 mm Hg, before upstream \( P_a \) or flow was affected, even though \( P_z=0 \) was between 50 and 60 mm Hg. Some of the discrepancy can be explained by the capacitance effects noted above, because when this is taken into account, \( P_b \) was only 42 mm Hg as compared with 54 mm Hg (Table 1) in the six animals with variable times to \( P_z=0 \). Another factor is that \( P_b \) represents the mean value of a family of critical pressures so that downstream changes in pressure could be transmitted by channels with low critical pressures. However, if this was the whole explanation, the variability of pressure in the compliant region in individual beds would have been very large. There is, however, a simpler explanation that is still completely consistent with the Starling resistor hypothesis and exactly what was predicted in the classic paper by Permutt and Riley on the "vascular waterfall." What must be remembered is that the bottom of the waterfall, or Starling resistor, can be a pressure upstream from the capillaries and not the pressure in the veins. Because there is a resistance between these two, this pressure can be higher than \( P_v \), and it is the difference between \( P_b \) and this pressure that determines the height of the waterfall. If the waterfall was approximately 10 mm Hg, as suggested by the average change in \( P_v \) before there was an upstream effect, and \( P_b \) was 42 mm Hg, then this pressure would be approximately 32 mm Hg, which is in the range of pressures that have been observed in the precapillary region (see Figure 31I of Reference 36) and is similar to the number predicted by Permutt and Riley in their analysis of Burton's data.

Another result that needs to be explained is the increase in \( P_z=0 \) with increases in \( P_v \). Bellamy and coworkers explained this by an increase in tissue pressure, which could thereby compress the region of the critical pressure and increase \( P_b \). Now, this result can be explained more easily by noting that an increase in \( P_v \) of sufficient magnitude to raise the pressure below the waterfall to \( P_b \) will remove the waterfall effect and begin to affect upstream vascular characteristics, as shown in Figures 4–7. Because flow was kept constant with a pump, when the increase in \( P_v \) overcame the waterfall, there had to be an increase in \( P_a \). \( P_z=0 \) would then increase because it is affected by \( P_a \) ("Appendix"). The second important point again comes from Permutt and Riley. When \( P_v \) is increased above the waterfall, the venous resistance must be added to the arterial resistance so that the total resistance increases and the slope of the pressure-flow line should decrease, which is in fact what was observed (Figure 8) in every case. Finally, \( P_z=0 \) decreased with reactive hyperemia and phenolamine. There are two factors that could explain this. First, the fall in \( P_a \) that occurred with both these maneuvers would have resulted in a decrease in \( P_z=0 \) ("Appendix"). Second, there was probably a decrease in arteriolar tone with both these maneuvers and therefore a decrease in the waterfall. In fact, increasing \( P_v \) had an immediate effect on upstream flow or pressure in all dogs except one after phenolamine treatment. The small decrease in \( P_a \) during muscle contraction could also have contributed to the decrease in \( P_z=0 \) in the exercising hind limb, as well as a decrease in pressure in the compliant region.

Dole et al. offered an alternative explanation for \( P_z=0 \). They invoked the presence of a variable middle resistance that would progressively increase as flow decreased. This could possibly be due to collapse of vessels and a loss of cross-sectional area as suggested in Burton's concept of critical closing pressures. Dole et al gave no explanation as to why the resistance decreases at a rate that produces a linear decrease in the pressure-flow relation. Furthermore, although their analysis successfully predicts the rightward shift of the pressure-flow relation with an increase in \( P_v \), it does not predict the decrease in slope that we observed. Finally, it does not readily explain the difference between the ramp decrease in flow and sudden occlusion of flow. Other explanations that have been invoked to explain vascular critical pressures have included effects from the hematocrit, interfacial tensions, myogenic mechanisms, and reflex adjustments.
Significance of a Starling Resistor Mechanism

Although these data support the presence of a Starling resistor mechanism in arterial vessels, the capacitance effect that was also observed has important implications for assessment of $P_z=0$. Thus, any pressure-flow measurement with less than 4 seconds for equilibration will have a significant capacitance component, and the measurements of $P_z=0$ by Dewey et al\textsuperscript{10} and Early et al\textsuperscript{11} in the cerebral circulation, Ehrlich et al in the kidney\textsuperscript{12} and hind limb,\textsuperscript{13} and Bellamy\textsuperscript{6} in the coronary circulation would significantly overestimate $P_b$. The same conclusions can be made about studies of autoregulation, such as those by Mosher et al\textsuperscript{25} in the coronary circulation, in which some of the autoregulatory effects could well have been capacitance effects. Also, the so-called "capacitance-free" measurements of Aversano et al,\textsuperscript{20} Carty et al,\textsuperscript{21} and Dole and Bishop\textsuperscript{27} may not have been completely capacitance-free, because we used a technique similar to that of Aversano et al\textsuperscript{28} and found that $P_z=0$ was still higher than the $P_b$ predicted by times to zero flow of 5–10 seconds.

The presence of a Starling resistor mechanism has some important implications for understanding the peripheral circulation. First, it implies that flow to different regions is determined by $P_a$ minus $P_b$ and the resistance between them rather than $P_a$ minus $P_v$ and the total resistance. The effective resistance is therefore less than the total resistance, and adjustment of $P_b$ is an important factor in the control of flow to different regions of the body; that is, flow can be altered by changes in $P_b$ or by changes in the arterial resistance. The presence of a Starling resistor mechanism also means that the capillary pressure, and therefore filtration pressures, can be adjusted without affecting the inflow to the region, because capillary pressures are below the waterfall. This would imply that the use of the ratio of upstream and downstream resistance for the assessment of capillary filtration is in fact an inaccurate way of assessing this pressure. The existence of a waterfall at the arteriolar level also means that the changes in $P_v$ that occur with respiratory maneuvers such as inspiration, a Valsalva maneuver, or a cough will not necessarily affect flow into the capillary bed, and thus, this mechanism helps maintain the stability of flow. Finally, the presence of a critical pressure means that with a sudden decrease in cardiac output, $P_a$ will not fall as rapidly as predicted by an analysis without a Starling resistor mechanism. This will, at least temporarily, help maintain flow to important areas such as the brain, which presumably have a lower critical pressure than resting muscle.

Appendix

Equations

\begin{align}
\frac{dV}{dt} & = Q_{in} - Q_{out} \quad (A1) \\
Q_{in} & = (P_l - P_c)/R_{in} \quad (A2)
\end{align}

\begin{align}
Q_{out} & = (P_c - P_b)/R_{out} \quad (A3) \\
V & = P_c C \quad (A4)
\end{align}

Combine Equations 1, 2, 3, and 4 to obtain

\begin{align}
\frac{dV}{dt} + V/R_{out}C & = Q_{in} + P_b/R_{out} \quad (A5) \\
Q_{in} & = Q_{t(0)} + \beta t \quad (A6)
\end{align}

Substitute Equation 6 in Equation 5 to obtain

\begin{align}
\frac{dV}{dt} + V/R_{out}C & = Q_{t(0)} + P_b/R_{out} + \beta \quad (A7)
\end{align}

Solve Equation 7 to obtain the solution for inflow equal to zero

\begin{align}
(P_z=0) & = P_b - \beta R_{out}^2 C(1 - e^{(Q_{t(0)}/R_{out}C)}) \quad (A8) \\
0 & = Q_{t(0)} + \beta (tz=0) \quad (A9) \\
(P_z=0) - P_b & = Q_{t(0)}R_{out} \tau (1 - e^{-tz=0/\tau}) \quad (A10)
\end{align}

but

\begin{align}
Q_{t(0)}R_{out} & = P_a - P_b \quad (A11) \\
(P_z=0) - P_b & = \frac{\tau}{P_a - P_b} (1 - e^{-tz=0/\tau}) \quad (A12)
\end{align}

when

\begin{align}
tz=0 >> \tau \quad (A13) \\
(P_z=0) - P_b & = \frac{\tau(P_a - P_b)}{tz=0} \quad (A14)
\end{align}

Symbols Used in Equations

\begin{align}
V & \text{ Stressed volume (ml)} \\
Q_{in} & \text{ Inflow (ml min$^{-1}$)} \\
Q_{out} & \text{ Outflow (ml min$^{-1}$)} \\
P_l & \text{ Inflow pressure (mm Hg)} \\
P_c & \text{ Pressure in compliant region (mm Hg)} \\
P_b & \text{ Back pressure (or outflow pressure) (mm Hg)} \\
P_a & \text{ Femoral arterial pressure (=PL) (mm Hg)} \\
C & \text{ Compliance (ml min Hg$^{-1}$)} \\
\beta & \text{ Slope of ramp change in flow (ml sec$^{-1}$ mm Hg$^{-1}$)} \\
t & \text{ Time (seconds)} \\
tz=0 & \text{ Time to zero flow (seconds)} \\
Q_{t(0)} & \text{ Flow in at time zero (ml min$^{-1}$)} \\
P_z=0 & \text{ Pressure at zero flow (mm Hg)} \\
R_{in} & \text{ Inflow resistance (mm Hg ml$^{-1}$ sec$^{-1}$)} \\
R_{out} & \text{ Outflow resistance (mm Hg ml$^{-1}$ sec$^{-1}$)} \\
\tau & \text{ R}_{out} \cdot C \text{ (seconds)}
\end{align}

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