Effect of Epinephrine on Pressure, Flow, and Volume Relationships in the Systemic Circulation of Dogs

By Paolo Caldini, Solbert Permutt, James A. Waddell, and Richard L. Riley

ABSTRACT
The effect of epinephrine on peripheral circulation was studied in ten anesthetized open-chest dogs. Blood flow and right atrial pressure were independently controlled by a right heart bypass; changes in blood volume could be precisely determined from the changes occurring in the bypass reservoir. At constant blood flow and right atrial pressure, a constant infusion of epinephrine (5.8 μg/kg min⁻¹) decreased blood volume by an average of 208 ml. During epinephrine infusion, the ratio of changes in blood volume to changes in blood flow measured at constant right atrial pressure, (ΔV/ΔQ)pr, decreased from 0.226 minutes to 0.153 minutes and the ratio of changes in blood volume to changes in right atrial pressure at constant blood flow, the vascular compliance, decreased from 27.1 ml/cm H2O to 20.7 ml/cm H2O. Transient changes in blood volume following a step decrease in right atrial pressure at constant blood flow showed that blood was draining from two vascular compartments with different time constants: 0.059 minutes and 0.388 minutes before epinephrine infusion and 0.058 minutes and 0.486 minutes during epinephrine infusion. We analyzed the data using a mathematical model of the peripheral circulation consisting of two compartments with different time constants. The analysis showed that the primary effect of epinephrine on the systemic circulation was to redistribute blood flow away from the compartment with the longest time constant. The reduction in (ΔV/ΔQ)pr and the decrease in blood volume at constant flow and right atrial pressure were essentially determined by the change in flow distribution brought about by a change in arteriolar tone and not by a change in venous tone.

KEY WORDS peripheral circulation vascular compliance cardiac output circulatory model venous resistance mean circulatory pressure venous return

For well over a hundred years, it has been recognized that the level of cardiac output is determined not only by the state of the heart but also by the state of the blood vessels (1,2). Grodins (3) has succinctly stated the reason behind this phenomenon: "...mechanical coupling between heart and circuit dictates that cardiac output is a function of both heart and circuit parameters." Guyton (4) has explained this relationship in more detail. The pressure of blood within the right atrium plays a unique role in the coupling between heart and blood vessels. On the one hand, the level of right atrial pressure relative to intrapleural pressure determines the filling pressure of the right ventricle. Therefore, right atrial pressure is intimately related to the degree of stretch of the right ventricle during diastole, which in turn affects the output of the right ventricle and thus that of the left ventricle (Starling's Law of the Heart). On the other hand, the level of right atrial pressure relative to atmospheric pressure determines the back pressure to perfusion for the systemic circulation.

Although much consideration has been given to the role of right atrial pressure in the determination of the filling pressure of the right ventricle, the effects of right atrial pressure in the determination of the back pressure to perfusion from the periphery have, in large part, been overlooked. It is apparent from the work of nearly everyone who has examined the control of cardiac output from the point of view of both the circuit and the pump (1-4) that, if circuit parameters (resistances and compliances along the entire course of individual blood vessels and total blood volume) remain fixed, the only way to increase cardiac output significantly through a change in heart parameters (heart rate, diastolic volume, and force of contraction) alone is to decrease right atrial pressure. Yet ample evidence indicates that a variety of cardiac outputs can occur at the same right atrial pressure (5).
In interpreting the mechanism underlying a marked increase in cardiac output with no significant change in right atrial pressure, circulatory physiologists have readily recognized a change in the way the heart contracts. However, a profound change in the state of the circuit must also occur. In a sense, the magnitude of the change in cardiac output in the presence of a constant right atrial pressure quantifies the magnitude of the changes in the circuit; moreover, this relationship suggests a way of evaluating the state of the periphery as one of the determinants of the cardiac output.

For instance, if the right ventricle were replaced or bypassed with a mechanical pump, the pump could be used to compensate for active changes in the periphery so as to maintain a constant right atrial pressure. Any change in steady-state blood flow would then reflect active peripheral changes if blood volume remained constant. In addition, if an external reservoir separated the right atrium and the mechanical pump, right atrial pressure could be controlled at any desired level, independent of changes in blood flow or peripheral parameters, simply by raising or lowering the reservoir. Under these conditions any active change in the periphery would be reflected by an increase or a decrease in the volume of the reservoir when blood flow and right atrial pressure are constant. In the present paper, we used just such a preparation to evaluate the peripheral effects of epinephrine on cardiac output.

To explain the peripheral effects of epinephrine on cardiac output, we described the changes in terms of a simple model of systemic circulation. The model assumed that all of the vascular compliance resides in the systemic circulation, specifically in the venous part of the system. This model distinctly differed from many current models of the circulation, because it placed a small but significant resistance between the compliant regions and the right heart; in this sense, the model relied heavily on the concepts developed by Guyton and his associates (6).

Initially, we modeled the systemic circulation as a single equivalent tube with all of the compliance lumped at a single locus between two resistors, the arterial resistance and the venous resistance. This model proved to be inadequate and was superseded by a slightly more complicated one involving two equivalent tubes, with different compliances and resistances, in parallel. The two parallel circuits were assumed to begin at the arteries and terminate at the major veins (Fig. 1). This model led to the surprising conclusion that an epinephrine-induced increase in steady-state venous return at constant right atrial pressure resulted from the drug's effect on the distribution of blood flow within the parallel channels. In other words, the significant effect of epinephrine was on the arterioles rather than the veins.

The present paper presents both a mathematical analysis of the model and an analysis of the experimental findings in terms of the model. Justification for the use of the model depends to a great extent on the experimental findings and will not be considered until the Discussion.

**Theory**

The model used in the analysis of the peripheral circulation consisted of two vascular compartments in parallel perfused by a single pump. The compliance of each vascular circuit was lumped in a single region between the arterial resistance and the venous resistance of the systemic circulation. Thus, the compliance of the peripheral circulation was considered to be principally in the small veins and venules; the compliances of the heart, the

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**FIGURE 1**

Model of the peripheral circulation with two vascular compartments in parallel. Ra = arterial resistance, C = compliant area, Rv = venous resistance, and the subscripts 1 and 2 indicate channels 1 and 2, respectively. Pra is the pressure existing at the inflow end of pump; it is analogous to right atrial pressure.
pulmonary vascular bed, the systemic arteries, and the large veins were neglected. The model for each individual circuit was somewhat analogous to Guyton's model of the systemic vascular bed in which the resistance to venous return is, in essence, the resistance downstream from the compliant region (7).

A representation of the model used in this paper is shown in Figure 1. The output of the pump was distributed to the two compartments by the two arterial resistors, \( R_a_1 \) and \( R_a_2 \). The compliances of channels 1 and 2 were at single loci, \( C_1 \) and \( C_2 \), respectively. Finally, the circuits were completed by two venous resistors, \( R_v_1 \) and \( R_v_2 \), which connected the compliant regions with the inflow end of the pump; the two circuits had no common venous resistance. The pressure existing at the inflow end of the pump, \( P_r_ a \), represented right atrial pressure.

STEADY-STATE CONDITIONS

Let us assume that \( R_a_1 \), \( R_a_2 \), \( R_v_1 \), and \( R_v_2 \) are constant and act as ohmic resistors. Therefore, for \( P_r_ a > 0 \),

\[
R_v_1 = \frac{P_s_1 - P_r_ a}{Q_1}, \quad (1a)
\]
\[
R_v_2 = \frac{P_s_2 - P_r_ a}{Q_2}, \quad (1b)
\]

where \( P_s_1 \) and \( P_s_2 \) are the pressures within the compliant regions and \( Q_1 \) and \( Q_2 \) are the flows through channels 1 and 2, respectively. When \( P_r_ a \leq 0 \), the large veins have the pressure-flow characteristics of a Starling resistor in which the pressure surrounding the collapsible tube is zero (8). Under these conditions, the effective downstream pressure is zero, and \( P_r_ a \) drops out of Eqs. 1a and 1b. Let us assume that the pressure-volume relationships of the compliant regions are linear and can be described as

\[
V_1 - V_0 = P_s_1 C_1, \quad (2a)
\]
\[
V_2 - V_0 = P_s_2 C_2, \quad (2b)
\]

where \( V_1 \) and \( V_2 \) are the volumes of the two compliant regions, \( V_0 \) and \( V_0 \) are their unstressed volumes, and \( C_1 \) and \( C_2 \) are the compliances of channels 1 and 2, respectively. Solving Eqs. 1a and 1b for \( P_s_1 \) and \( P_s_2 \), substituting their values in Eqs. 2a and 2b, and rearranging terms yields

\[
V_1 - V_0 = Q_1 R_v_1 C_1 - C_1 P_r_ a = 0, \quad (3a)
\]
\[
V_2 - V_0 = Q_2 R_v_2 C_2 - C_2 P_r_ a = 0. \quad (3b)
\]

Let \( Q_1 + Q_2 = Q \), the total blood flow through the circuit, \( V_1 + V_2 = V \), the total volume of the compliant regions, and \( V_0 + V_0 = V_0 \), the total unstressed volume of the compliant regions. Let \( Q_1/Q = F_1 \) and \( Q_2/Q = F_2 \). Thus, \( F_1 \) and \( F_2 \) are the fractional flows through channels 1 and 2, respectively, and their sum is unity. Thus, \( Q_1 = F_1 Q \) and \( Q_2 = F_2 Q \). Substituting these values into Eqs. 3a and 3b and adding the two equations yields the following general equation:

\[
(V - V_0) - (F_1 R_v_1 C_1 + F_2 R_v_2 C_2) \dot{Q} - (C_1 + C_2) P_r_ a = 0. \quad (4)
\]

Eq. 4 yields the partial derivatives

\[
\frac{\partial V}{\partial P_r_ a} = C_1 + C_2, \quad (5)
\]
\[
\frac{\partial Q}{\partial P_r_ a} = F_1 R_v_1 C_1 + F_2 R_v_2 C_2, \quad (6)
\]
\[
\frac{\partial P_r_ a}{\partial Q} = -\left( F_1 R_v_1 C_1 + F_2 R_v_2 C_2 \right)/(C_1 + C_2). \quad (7)
\]

FIGURE 2

Relationships among volume (V), flow (Q), and right atrial pressure (Pra). For additional explanations of symbols see text.
where the ratios within the initial parentheses are the partial derivatives which apply when the third variables (represented by the subscripts outside the parentheses) are constant. The relationships among V, Q, and Pra from Eq. 4 and the slopes from Eqs. 5–7 are shown in Figure 2.

If volumes, compliances, and resistances are held constant and the relationship between Q and Pra is plotted, Eq. 4 can be arranged as

$$\dot{Q} = (P_s - Pra)/R_v,$$

when Pra > 0, and as

$$\dot{Q}_{max} = P_s/R_v,$$

when Pra ≤ 0. $\dot{Q}_{max}$ is the maximum possible flow at constant Ps and Rv, and Ps and Rv are constants defined as

$$-dV_i/dt = [V_i(t) - (Vo_i + Ps_i)/C_i]$$(10a)

$$R_v = (F_1R_vC_1 + F_2R_vC_2)/(C_1 + C_2).$$ (10b)

Ps and Rv in Eq. 8 are, in the terminology of Guyton et al. (6), mean systemic pressure and resistance to venous return, respectively.

In the studies reported in this paper, measurements of the steady-state ratios indicated in Eqs. 5 and 6 were carried out. The steady-state ratio in Eq. 7, which is theoretically equivalent to Rv as it is defined by Guyton et al. (6), was not measured directly but was calculated from Eqs. 5 and 6 as shown in Eq. 7. By substituting this value of Rv in Eq. 8 at known values of $\dot{Q}$ and Pra, Ps was calculated (Fig. 2c).

$$\frac{V_i(t) - V_{i(ss)}}{V_i(t) - V_{i(ss)}} = \left[\frac{V_i(t) - V_{i(ss)}}{V_i(t) - V_{i(ss)}}\right] e^{-R_vC_1},$$

where $V_i(t)$ is the initial volume of the compliant region. Similarly for channel 2

$$\frac{V_2(t) - V_{2(ss)}}{V_2(t) - V_{2(ss)}} = \left[\frac{V_2(t) - V_{2(ss)}}{V_2(t) - V_{2(ss)}}\right] e^{-R_vC_2}.$$ (15)

Adding Eqs. 14 and 15 and dividing by $[V_i(t) - V_{i(ss)}]$ yields

$$\frac{[V_i(t) - V_{i(ss)}]}{[V_i(t) - V_{i(ss)}]} = \frac{C_1}{C_1 + C_2}.$$ (16)

It can be shown that the two terms in the brackets are equal to $C_1/(C_1 + C_2)$ and $C_2/(C_1 + C_2)$, respectively, because

$$\Delta P_s = \Delta P_{s_2} = \Delta Pra,$$

between the steady states before and after a step change in Pra at constant flow, and

$$V_i(t) - V_{i(ss)} = C_1\Delta Pra,$$

$$V_{2(t)} - V_{2(ss)} = C_2\Delta Pra,$$

$$V(t) - V_{(ss)} = (C_1 + C_2)\Delta Pra.$$ Hence,

$$e^{-R_vC_1} + \left[C_2\left(\frac{C_1}{C_1 + C_2}\right)\right] e^{-R_vC_2}.$$ (17)

A semilogarithmic plot of the changes with the reservoir must be introduced between the right atrium and the inflow to the pump.

Any change in the volume of the compliant regions must be accompanied by an opposite change in the volume of the reservoir. Thus, the rate of change in volume of a compliant region is equal to the inflow to minus the outflow from this region. For channel 1:

$$dV_i/dt = \dot{Q}_1 - [P_{s_1(t)} - Pra]/R_v,$$

where $\dot{Q}_1$ is the inflow into compliant region 1 and $P_{s_1(t)}$ is the pressure in compliant region 1 at time t. Therefore, $[P_{s_1(t)} - Pra]/R_v$ is the outflow from compliant region 1 at time t. Substituting $[V_{i(t)} - Vo_i]/C_1$ for $P_{s_1(t)}$ (from Eq. 2) and rearranging terms yields

$$-dV_i/dt = [V_{i(t)} - V_{i(ss)}]/R_vC_1.$$ (13)

Integrating Eq. 13 and solving for the constant of integration yields

$$[V_{i(t)} - V_{i(ss)}] = [V_{i(t)} - V_{i(ss)}] e^{-R_vC_1}$$

where $V_{i(t)}$ is the initial volume of the compliant region. Similarly for channel 2

$$[V_{2(t)} - V_{2(ss)}] = [V_{2(t)} - V_{2(ss)}] e^{-R_vC_2}.$$ (15)

Adding Eqs. 14 and 15 and dividing by $[V_i(t) - V_{i(ss)}]$ yields

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between the steady states before and after a step change in Pra at constant flow, and

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where $V_{i(t)}$ is the initial volume of the compliant region. Similarly for channel 2

$$[V_{2(t)} - V_{2(ss)}] = [V_{2(t)} - V_{2(ss)}] e^{-R_vC_2}.$$ (15)

Adding Eqs. 14 and 15 and dividing by $[V_i(t) - V_{i(ss)}]$ yields

$$\frac{[V_i(t) - V_{i(ss)}]}{[V_i(t) - V_{i(ss)}]} = \frac{C_1}{C_1 + C_2}.$$ (16)

It can be shown that the two terms in the brackets are equal to $C_1/(C_1 + C_2)$ and $C_2/(C_1 + C_2)$, respectively, because

$$\Delta P_s = \Delta P_{s_2} = \Delta Pra,$$

between the steady states before and after a step change in Pra at constant flow, and

$$V_i(t) - V_{i(ss)} = C_1\Delta Pra,$$

$$V_{2(t)} - V_{2(ss)} = C_2\Delta Pra,$$

$$V (t) - V_{(ss)} = (C_1 + C_2)\Delta Pra.$$ Hence,

$$e^{-R_vC_1} + \left[C_2\left(\frac{C_1}{C_1 + C_2}\right)\right] e^{-R_vC_2}.$$ (17)

A semilogarithmic plot of the changes with the reservoir must be introduced between the right atrium and the inflow to the pump.
Semilogarithmic plot of the ratio of blood volume still to change at time \( t \), \((V_t - V_w)\), to the total volume change between two steady states \((V_i - V_w)\) as a function of time following a step decrease in right atrial pressure at constant blood flow. Actual data from one of the experimental dogs.

time in the ratio on the left of Eq. 17 is shown in Figure 3, where \( R_v C_2 > R_v C_1 \). Unlike the plot for a one-channel model, the relationship is curvilinear, but it becomes essentially linear with increasing time. It would have been linear throughout if \( R_v C_2 = R_v C_1 \). If the linear portion of Figure 3 is extrapolated back to \( t = 0 \), the intercept on the ordinate is equal to \( C_2/(C_1 + C_2) \). If the derived straight line is subtracted from the curve, another straight line is obtained which intercepts the ordinate at a value equal to \( C_1/(C_1 + C_2) \). The time required for the straight line starting from \( C_2/(C_1 + C_2) \) to reach a value of \((1/e)(C_1)/(C_1 + C_2)\), or approximately \(0.37C_1/(C_1 + C_2)\), is \( R_v C_1 \). Likewise, the time required for the straight line starting from \( C_2/(C_1 + C_2) \) to fall to a value of \(0.37C_2/(C_1 + C_2)\) is \( R_v C_2 \).

DETERMINATION OF THE PARAMETERS OF THE TWO-CHANNEL MODEL WITH AN EXTERNAL RESERVOIR AT THE INFLOW END OF THE PUMP

The sum of the volume changes of both compliant regions was determined from the volume changes of the external reservoir. After the steady-state change in the volume of the compliant regions following a change in \( Q \) at constant \( P_{ra} \) and both the steady-state and the transient changes in volume after a step change in \( P_{ra} \) at constant \( Q \) were determined, \( C_1, C_2, R_{v1}, R_{v2}, F_1 \), and \( F_2 \) could be calculated. \((C_1 + C_2)\) was calculated from the steady-state values before and after a step change in \( P_{ra} \) at constant \( Q \) utilizing Eq. 5 (Fig. 2a). From the intercepts of the two derived lines on a semilogarithmic plot of Eq. 17 and the values of \((C_1 + C_2)\), \( C_1 \) and \( C_2 \) were individually calculated (Fig. 3). \( R_v C_1 \) and \( R_v C_2 \) were calculated from the times required for the two derived lines on the semilogarithmic plot to fall to values 0.37 of their values at \( t = 0 \) (Fig. 3). From these latter calculations and \( C_1 \) and \( C_2 \), \( R_{v1} \) and \( R_{v2} \) were calculated. From the measured value of \((\Delta V/\Delta Q)_P \) and the calculated values of \( R_{v1}, R_{v2}, C_1 \), and \( C_2, F_1 \) and \( F_2 \) were calculated from Eq. 6 (Fig. 2b). From \( F_1, F_2, Q, P_{s1} \), (from Eq. 1a), \( P_{s2} \) (from Eq. 1b), and arterial blood pressure, \( R_a1 \) and \( R_a2 \) were calculated from Ohm’s Law applied to parallel circuits.

Methods

Mongrel dogs (14–29 kg) were anesthetized with sodium pentobarbital (30 mg/kg, iv). Additional small amounts of the anesthetic were administered to the dogs when required. The trachea was cannulated and connected to a constant-volume respirator (Harvard pump); a constant tidal volume of 200 ml plus 5 ml/kg body weight at a respiratory rate of 18 breaths/min was maintained in each experiment. End-expiratory pressure was maintained at 5 cm H₂O by immersing the expiratory line of the respirator in water. A thoracotomy was performed by longitudinally splitting the sternum. Following administration of sodium heparin (3 mg/kg body weight), a large-bore cannula with multiple holes at the tip was introduced into the right atrium. While the dog was on bypass, the blood returning to the right atrium was allowed to drain by gravity into a heated reservoir through a thin-walled collapsible tube connected to the right atrial cannula (Fig. 4). It was possible to change right atrial pressure over a rather wide range by raising or lowering the height of the collapsible tube. From the reservoir, blood was returned to the dog by a Sarns roller pump via a cannula placed in the main pulmonary artery through the outflow tract of the right ventricle. By placing a ligature around the pulmonary artery with the cannula inside, the blood flow perfusing the pulmonary and systemic circulations under steady-state conditions was determined by the output of the pump.
which could be controlled at will. The inevitable small collection of blood inside the chest cavity owing to surgical procedures in the heparinized dogs was continuously pumped back into the venous reservoir from two cannulas introduced into the two hemithoraces. The change in the volume of blood in the reservoir was indicated by the pressure change at the bottom of the reservoir and was continuously recorded. The change in reservoir volume was interpreted as the inverse of the change in the dog's blood volume. A pressure-recording catheter was introduced into the right atrium through a femoral vein. Pulmonary arterial, left atrial, and femoral arterial pressures were also monitored to test the stability of the preparation. Right atrial pressure was recorded with a Statham P23BB pressure transducer at high sensitivity (1 cm H_2O = 2.5 cm paper). The zero reference point was the level of the tip of the right atrial catheter. This level was determined at the end of each experiment by opening the right atrium and exposing the tip of the right atrial catheter to atmospheric pressure while the catheter was still in place. Blood flow was measured with a resistance flowmeter interposed in the outflow tube of the pump, and the lateral pressures at each side of the resistive tube were recorded using two separate Statham P23De pressure transducers adjusted to equal sensitivity.

When the effect of epinephrine on the systemic circulation was studied, epinephrine was given as a constant infusion (2-7.1 \( \mu \)g/kg min\(^{-1} \)), mean 5.8 \( \mu \)g/kg min\(^{-1} \)) into a peripheral vein.

Steady-state values, \( \Delta V/\Delta Q \) and \( \Delta V/\Delta P_{ra} \), were repeatedly measured in all the dogs before and during epinephrine infusion. \( \Delta V/\Delta Q \) was obtained by changing the output of the pump and observing the change in blood volume when a new steady state was reached. In general, the flow was increased by approximately 25% of the initial steady-state blood flow and subsequently lowered to the initial level. The compliance of the peripheral vascular bed was measured by changing right atrial pressure approximately 6 cm H_2O while pump output was kept constant and observing the change in reservoir volume after a new steady state was reached. Changes in right atrial pressure were obtained by raising and lowering the Starling resistor connected to the right atrial cannula.

The transient changes in blood volume at constant flow were measured following a step decrease in right atrial pressure from 6 cm H_2O to approximately 1 cm H_2O. The difference between the final steady-state blood volume, \( V_{1}(m) \), and the volume at any given time, \( V_{1} \), was divided by the total volume change, \( V_{1}(m) - V_{1}(m) \). This ratio was plotted against time on semilogarithmic paper. The volume changes in the reservoir could be measured with sufficient precision to carry the plot a little beyond one decade on the logarithmic scale. The curves did not prove to be single exponentials, but excellent fits were achieved with two exponentials (Fig. 3).

As seen in Figure 4, a segment of tubing was interposed between the right atrium and the Starling resistor by which \( P_{ra} \) was changed. Since venous blood returned first to the right atrium and passed through the tubing on the way to the Starling resistor, the resistance of the tubing had to be considered in performing experiments to measure transient changes. The time constants of the two compartments were corrected for the additional resistance of the right atrial cannula and tubing by subtracting from each time constant the product of the cannula resistance (mean value = 1.65 cm H_2O/liter min\(^{-1} \)) and the compartment compliance. This correction is only an approximation, but it is quite accurate when the common resistance is small in relation to the parallel venous resistances. For an average experiment, the common resistance was approximately 30% of the total parallel resistance. Under these conditions, the applied correction resulted in less than a 2% underestimation of the fast time constant and less than a 0.2% overestimation of the slow time constant.

Pressure-volume curves for the peripheral vascular bed were studied in nine dogs by measuring the change in blood volume brought about by a change in right atrial pressure. Right atrial pressure was increased from 0 cm H_2O to 10-15 cm H_2O in increments of 2 cm H_2O and then lowered back to 0 cm H_2O in similar decrements. At each level, the right atrial pressure was kept constant until a new quasi-steady state in blood volume was obtained. Some hysteresis was invariably observed in the construction
of the pressure-volume curves: the changes in blood volume were smaller when pressure was lowered than they were when it was raised an equal amount. Because of this hysteresis only the composite ascending limb of the pressure-volume curve was reported.

Arterial pH, PCO₂, and PO₂ were measured occasionally during the study. If a decrease in blood pH was noted, it was corrected by an infusion of NaHCO₃ solution.

Only 10 of 14 attempted right heart bypasses were successful. If appreciable blood loss or periods of systemic hypotension were encountered during the procedure or if the blood volume failed to remain stable, the preparation was discarded before any measurements were made. Collection of control data was not initiated until 30 minutes after the successful establishment of a bypass perfusion. Usually within this time the preparation became stable, as indicated by a constant volume of blood in the reservoir and a constant arterial blood pressure when blood flow and atrial pressure were kept constant.

**Results**

**STEADY-STATE MEASUREMENTS**

In the ten dogs studied, the ratio of the change in blood volume to the change in blood flow measured at constant right atrial pressure, \( \frac{\Delta V}{\Delta Q}_{pra} \), was 0.226 ± 0.030 (SE) minutes and during epinephrine infusion the ratio decreased significantly to 0.153 ± 0.018 minutes (\( P < 0.01 \)) (Table 1, Fig. 5).

Vascular compliance, \( \frac{\Delta V}{\Delta P_{ra}} \), was 27.1 ± 3.9 (SE) ml/cm H₂O (1.29 ± 0.10 ml/cm H₂O kg⁻¹), and during epinephrine infusion it decreased to 20.7 ± 2.6 ml/cm H₂O (0.96 ± 0.06 ml/cm H₂O kg⁻¹) (\( P < 0.01 \)).

No consistent change in the resistance to venous return, \( \frac{\Delta P_{ral}}{\Delta Q} \), was observed during epinephrine infusion. The mean resistance before the epinephrine infusion was 8.85 ± 1.40 cm H₂O/liter min⁻¹, and during epinephrine infusion it was 7.94 ± 1.01 cm H₂O/liter min⁻¹.

At constant right atrial pressure and blood flow, a constant infusion of epinephrine increased mean arterial blood pressure by an average of 47% of the control value in spite of a decrease in blood volume averaging 208 ml (Table 1).

\( P_s \) after epinephrine infusion was calculated from Eq. 8. If no change in blood volume had occurred, \( P_s \) after the epinephrine infusion would have been increased over this value by an amount \( \Delta P_s \), which is equal to

\[
\Delta P_s = \Delta V/(C_1 + C_2)_{eq},
\]

(18)
EPINEPHRINE AND THE PERIPHERAL CIRCULATION

where \((C_1 + C_2)_{epi}\) is the total compliance during epinephrine infusion. During epinephrine infusion \(P_s\) rose from \(13.8 \pm 1.58\) (SE) cm H₂O to \(24.6 \pm 2.84\) cm H₂O, an increase of \(78\%\) (\(P < 0.01\)) (Table 1, Fig. 5). The \(Q_{max}\) which would have existed under isovolumic conditions after epinephrine infusion was calculated from Eq. 9.

It rose from \(1.69 \pm 0.15\) (SE) liters/min to \(3.38 \pm 0.51\) liters/min (\(P < 0.02\)) (Table 1, Fig. 5).

TRANSIENT MEASUREMENTS

At a constant pump output, the effects of a step decrease in right atrial pressure on transient changes in blood volume were studied in six of the dogs.

TABLE 2

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>(R_1C_1) (minutes)</th>
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<th>(C_1) (ml/cm H₂O)</th>
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NS = not significant.

Circulation Research, Vol. XXXIV, May 1974
the ten dogs. Figure 6 and Table 2 show the time constants, compliances, and resistances of the two vascular compartments before and during epinephrine infusion. The changes in mean values for the fast compartment were minimal. Epinephrine increased the mean time constant 25%, decreased the compliance 31%, and increased resistance 112% in the slow compartment. Only the decrease in compliance was statistically significant ($P < 0.02$). Calculation of the amount of blood flow through the two vascular compartments revealed that before the epinephrine infusion slightly more than half of the blood flowed through the compartment with a long time constant, but during the epinephrine infusion most of the blood flow was diverted away from this compartment. The decrease in blood flow through the slow compartment was from 54% to 27% of total flow, whereas the increase in flow through the fast compartment was from 46% to 73% (Fig. 6, Table 2). The changes in distribution were statistically significant ($P < 0.005$). There was a statistically significant increase in the arteriolar resistance of the compartment with the long time constant during epinephrine infusion ($P < 0.02$), but no statistically significant change in the arteriolar resistance occurred in the compartment with the short time constant even though the mean arteriolar resistance of the fast compartment decreased (Fig. 6, Table 2).

**PRESSURE-VOLUME CURVES**

Figure 7 illustrates the composite ascending limb of the pressure-volume curves obtained before and during epinephrine infusion in nine dogs studied while they were on right heart bypass. All curves were normalized to that of a 20-kg dog. The average curve during epinephrine infusion was displaced downward on the volume axis by 208 ml at $P_{\text{ra}} = 2.1$ cm H$_2$O. In all the dogs studied, the curves showed a convexity toward the pressure axis. The slope of the pressure-volume curve during epinephrine infusion was consistently less than that of the control curve at any given right atrial pressure.

**SEPARATION OF EFFECTS OF EPINEPHRINE ON ELASTIC AND RESISTIVE PROPERTIES FROM THOSE ON DISTRIBUTION OF BLOOD FLOW BETWEEN COMPARTMENTS**

The mean $Q$ and $P_{\text{ra}}$ for all experiments before and during epinephrine infusion were 1.43 liters/min and 2.13 cm H$_2$O, respectively. Mean values for $(\Delta V/\Delta Q)_{\text{ra}}$ and $(\Delta V/\Delta P_{\text{ra}})_{\text{ra}}$ before and during epinephrine infusion and the mean decrease in blood volume during epinephrine...
EPINEPHRINE AND THE PERIPHERAL CIRCULATION

Using the mean values of $R_0C_1$ and $R_0C_2$ before and during epinephrine administration, the effects of epinephrine under conditions in which the distribution of flow was assumed to be constant were compared with those under conditions in which a change in distribution occurred.

Figure 8 shows the relationship among volume, initial unstressed volume, and mean systemic pressure. This relationship represents the static pressure-volume characteristics of the systemic vascular bed. Epinephrine shifted the curve to the right; unstressed volume decreased 91 ml and the slope decreased slightly. The points from Figure 7 (omitting the lowest values) were included after conversion of $Pra$ to $Ps$. The 208-ml decrease was due to a shift from one curve to the other with a small decrease in $Ps$. $Ps$ decreased at constant $Q$ and $Pra$ due to the small decrease in resistance to venous return, $(\Delta P_{ra}/\Delta Q)_v$. If the distribution of flow had remained constant, $Ps$ would have had to increase 7 cm H$_2$O to keep $Q$ constant at constant $Pra$. Under these conditions, only 35 ml would have moved to the reservoir instead of 208 ml because of the large increase in resistance to venous return, $(\Delta P_{ra}/\Delta Q)_v$. Eq. 7 shows the marked influence of the distribution of flow on resistance to venous return. Epinephrine distributed more blood flow to the compartment with lower compliance and resistance, and, by this redistribution alone, caused 173 ml of the total 208 ml of blood to move to the reservoir from the compartment with the greater compliance and resistance. Thus, the net effect of the change in flow distribution on blood volume at constant $Q$ and $Pra$ consisted of 173 ml of the 208-ml decrease caused by epinephrine.

If the isovolumic conditions were maintained during the administration of epinephrine, the relationships between $Q$ and $Pra$ are those shown in Figure 9. This curve is Guyton's venous return curve from the mean data analyzed in terms of the two-compartment model. Epinephrine increased $Ps$ from 14.0 to 22.8 cm H$_2$O and increased the slope slightly, i.e., resistance to venous return fell from 8.3 to 7.4 cm H$_2$O/liter min$^{-1}$, and $Q_{max}$ increased from 1.68 to 3.08 liters/min. Note that these values are close to the mean values in Table 1, but they were calculated in a different manner.

Even if there had been no change in the distribution of flow, the effect of epinephrine on $Ps$
**FIGURE 8**

Static pressure-volume relationship of the peripheral circulation before and during epinephrine infusion. Changes in blood volume (V) and mean systemic pressure (Ps) due to either changes in distribution or changes in elastic and resistive properties are shown. Mean values ± 1 SE from the measured pressure-volume curves are included after conversion of Pra to Ps.

**FIGURE 9**

Relationship between flow (Q) and right atrial pressure (Pra) before and during epinephrine infusion calculated for isovolumic conditions. Broken line represents the effect of epinephrine on the elastic and resistive properties alone.

would have been the same, since this variable depends only on volume and elastic properties (Eqs. 10a and 10b). Resistance to venous return would have increased from 7.4 to 13.2 cm H₂O/liter min⁻¹ without the change in distribution. Thus, Qmax would have remained essentially unchanged; therefore, the entire increase in Qmax can be considered to be the result of changes in distribution. Note, however, that at high right atrial pressures changes in elastic properties alone would have caused significant increases in Q.

Figure 10 shows the relationship between Qmax and Ps with the slope of the lines equal to the reciprocal of the resistance to venous return.

Figure 11 shows the relationship between Qmax and V. Epinephrine shifted the curve vertically and increased the slope. Thus, at constant volume, the cardiac output attainable.
with maximum cardiac function was increased. Without a change in distribution of blood flow, this effect is minimal except at very low blood volumes.

**Discussion**

**JUSTIFICATION FOR USE OF MODEL**

Guyton et al. (9) have determined venous return curves in dogs before and after administration of epinephrine, and our constructed venous return curves (Fig. 9) are strikingly similar in terms of both absolute values and changes in mean systemic pressure and resistance to venous return. Nevertheless, the method we used was entirely different; we generated small changes in blood volume through small changes in either right atrial pressure or blood flow, assumed linearity of pressure-volume and pressure-flow relationships, and determined mean systemic pressure by extrapolation. The similarity of findings from entirely different methods suggests that the systemic vascular bed can be treated as a quasi-linear system, at least when the relationships among mean systemic pressure, volume, and flow are considered. These assumptions are supported by the work of Guyton et al. (6); they found nearly linear venous return curves and relationships between mean systemic pressure and volume.

The similarity of our constructed venous return curves to those directly measured by Guyton et al. (9) presented us with a dilemma which led us to the two-compartment model. In both studies, epinephrine caused a slight decrease in the resistance to venous return. How could venous tone be sufficiently increased to cause a large increase in mean systemic pressure without also causing an increase in the resistance to venous return? Guyton et al. suggested that the veins could not constrict unless vessels elsewhere were dilated, since their studies were carried out under isovolumic conditions and since blood is incompressible. Because the effect of epinephrine is probably even more marked on the arteries and arterioles than it is on the veins of the systemic circulation, they did not think that it was surprising to have a slight decrease in the resistance to venous return.

The explanation given by Guyton et al. is not suitable for our results. In our studies, the administration of epinephrine caused, on the average, a decrease in blood volume of more
than 200 ml. The only likely place that much of this blood could have come from was the systemic veins; therefore, they must have been smaller. Yet the resistance to venous return did not increase and even decreased slightly. The two-compartment model handles this dilemma very nicely; the slope of the venous return curve—the resistance to venous return—is markedly affected by changes in the distribution of flow between the two compartments (Eq. 7). Distribution is determined almost entirely by changes in arteriolar resistance.

Determination of the parameters of the two hypothetical compartments individually (if indeed two compartments exist) necessitated making transient measurements of volume following some forcing of the system. We chose to cause a step decrease in right atrial pressure at constant flow, because in our experimental preparation this procedure was easier and more accurate than a step change in flow at constant right atrial pressure. Furthermore, the curve-peeling technique would immediately provide data not only on the two time constants but also on the ratio of the two compliances (Eq. 17).

When the transient measurements were carried out, the relationships between volume and time could only be accounted for by the sum of two exponentials of widely different time constants; moreover, no more than two exponentials were necessary to account for the data over a range greater than one decade (Fig. 3). These findings are compatible with the proposed two-compartment model, but there are other possible explanations.

The transient findings alone can be accounted for by a two-compartment model in series as is shown in Figure 12. The transient equations for such a model are as follows: ²

\[ 1/\tau_{fast} = \left[ \alpha + (\alpha^2 - 4\beta)^{1/2} \right]/2, \]
\[ 1/\tau_{slow} = \left[ \alpha - (\alpha^2 - 4\beta)^{1/2} \right]/2, \]

where \( \tau_{fast} \) is the time constant of the fast transient, \( \tau_{slow} \) is the time constant of the slow transient, and

\[ \alpha = \left[ \left( \frac{1}{(Ru/Rd)} \right) (RuCu) / (RuCu + RdCd) \right] + 1/RuCu, \]
\[ \beta = 1/((RdCd)(RuCu)), \]

where \( Cu \) and \( Cd \) are the upstream and downstream compliant areas, respectively, and \( Ru \) and \( Rd \) are the upstream and downstream resistances, respectively.

The steady-state \((AV/\Delta Q)_{Pr} \) is

\[ (AV/\Delta Q)_{Pr} = [(Ru + Rd)/(RuCu)] + RdCd. \]

The fraction of the total volume which leaves slowly is \((1/\tau_{fast} - 1/\tau_{slow})/\tau_{fast} - 1/\tau_{slow})\), where \( \tau = (Rd/Ru)RuCu + RdCd. \)

There is no solution to this equation which allows \((AV/\Delta Q)_{Pr} \) to be smaller than the time constant for the slower transient, yet the experimental results clearly show that \((AV/\Delta Q)_{Pr} \) is much smaller. The only linear model that can account for this combination of findings is a long-time constant area in parallel with a short-time constant area.

Based on this analysis and the transient and steady-state data, the inescapable conclusion is that there must be an area with a long time constant in parallel with an area with a much shorter time constant with each area receiving only part of the cardiac output. This conclusion does not mean, however, that there are not effective compartments in series.

Our analysis ignores the pulmonary circulation, but the pulmonary circulation cannot affect

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Mathematical derivations for these formulas have been deposited with the American Society for Information Service, National Auxiliary Publications Service. Photoprint or microfilm copies are available at a moderate cost.
these conclusions. If pulmonary circulation had significant compliance, then the measured \((\Delta V/\Delta Q)_{pra}\) would be somewhat larger than \((\Delta V/\Delta Q)_{pra}\) for the systemic circulation alone. This simplification would lead to overestimation of the fraction of the blood flow which goes to the long-time constant area, but there would still have to be a long-time constant area in parallel in the systemic circulation to account for the results.

Further work now in progress suggests that very little would be added by considering the pulmonary circulation. We have carried out two experiments using a preparation with combined right and left heart bypass and two reservoirs so that \((\Delta V/\Delta Q)_{pra}\) for the systemic circulation alone could be calculated. These values both before and during epinephrine administration were within the same range as those for the experiments reported in this paper, and the mean values for these two studies were only slightly lower than those obtained with right heart bypass alone. Still other studies are now being carried out in the total-bypass preparation under isovolumic conditions, i.e., venous return curves are being constructed by elevating right atrial pressure at constant left atrial pressure and elevating left atrial pressure at constant right atrial pressure. Left atrial pressure has to be elevated 8-10 times more than right atrial pressure to generate an equal reduction in venous return, which suggests that the compliance of the pulmonary circulation is nearly an order of magnitude less than that of the systemic circulation.

These same considerations apply to the compliance of the systemic arteries, which we have ignored in our model. Guyton et al. (10) estimated that arterial compliance was about 1/18 of systemic vascular compliance. Recent studies by Shoukas and Sagawa (personal communication) suggest that the value is nearer 1/30. In our studies, the small increases in flow used to measure \((\Delta V/\Delta Q)_{pra}\) were associated with only small changes in arterial blood pressure so the arteries could not have contributed more than a negligible amount to the values that we obtained.

Unquestionably, the large veins effectively add a series compliance, but mathematical analysis of a combined parallel series model shows that this addition has little effect on the accuracy of the measurements of the parallel slow-time constant area. It does result in overestimation of the fast time constant, however. The same considerations apply if the large veins contribute a resistance in series. Our model does not consider series resistance downstream from the confluence of the two parallel compartments. We feel relatively confident about the quantification of the very slow parallel time constant in the systemic circulation, but the time constant of the fast compartment might have been overestimated. Even a fast-compartment time constant of zero would hardly affect the results: \(F_2\) would change from 0.61 to 0.34 during infusion of epinephrine rather than from 0.55 to 0.25.

Any drainage from the extravascular fluid compartment would not significantly contribute to the estimation of the slow time constant, for this system is analogous to the series model. Under these conditions, the steady-state changes in \((\Delta V/\Delta Q)_{pra}\) would have been larger, not smaller, than the time constant of the slow transient.

Finally, the combination of the steady-state and transient changes taken together effectively rules out the model of Grodins et al. (11) in which the total peripheral resistance is lumped between the arterial and the venous compliances. Essentially, the same model was used by Folkow and Neil (12). Not only would \((\Delta V/\Delta Q)_{pra}\) be greater than the long time constant, but a step change in right atrial pressure at constant flow would cause a nearly instantaneous volume change. The arteries, which have a finite time constant, could contribute only a very small amount of the total volume \((1/18 \text{ to } 1/30)\). Yet in our studies, more than 50% of the volume left with a very long time constant (greater than 0.3 minutes). Bartelstone (13) has found that, on occlusion of the descending aorta, venous runoff through the inferior vena cava continues unaffected for 5 seconds and diminishes only slightly over the next 5 seconds. This finding certainly means that the time constant of venous drainage must be considerably in excess of 0.17 minutes. He further found that the arteries contributed essentially nothing to the runoff. Bartelstone (13) was forced to conclude that the venous system is composed of a large compliant peripheral reservoir connected to a "central venous conduit" which offers resistance to the flow of blood and that the compliance of arteries is negligible. This model is essentially the one that we used for each of the two compartments.

WHERE ARE THE COMPARTMENTS?

The present studies shed no light on the loca-
tion of the two compartments. It seems highly likely though that the splanchnic circulation is one of the main components of the slow-time constant area. Bradley (14) has reviewed the long history of widely held ideas concerning the splanchnic circulation as a reservoir which is involved in the control of cardiac output. Suffice it to state that the evidence is good. What is even more significant, there is considerable evidence dating back to Poiseuille in 1832 (14) that changes in splanchnic blood flow can significantly affect the pressure in mesenteric veins independent of changes in the venous outflow pressure of the splanchnic circulation.

The potential role of the splanchnic venous reservoir in the control of cardiac output was presented by Krogh in 1912 (15). He used a two-compartment model similar to ours and showed how a decrease in blood flow to the splanchnic circulation could lead to a significant increase in cardiac output.

A similar two-compartment model was used by Barcroft and Samaan (16) to account for the paradoxical increase in cardiac output seen following the clamping of the descending thoracic aorta of the dog, which would be expected to divert blood away from the splanchnic circulation.

We are currently extending the studies of Barcroft and Samaan. In one experiment with a right heart bypass and an attached reservoir, clamping the descending thoracic aorta decreased \( \Delta V/\Delta \dot{Q}_{pra} \) from 0.155 to 0.074 minutes. This decrease was accompanied by a decline in blood volume of 168 ml, a decrease in resistance to venous return from 11 to 4 cm H\(_2\)O/liter min\(^{-1}\) in spite of the decrease in volume, and only minimal changes in the parameters associated with the two compartments except for the distribution of flow. \( F_1 \) increased from 0.43 to 0.97 and \( F_2 \) decreased from 0.57 to 0.03. The model closely predicted the amount of blood which entered the reservoir.

If clamping the descending aorta brings about the increase in cardiac output merely by diverting blood away from the long-time constant area, venous return curves constructed by Guyton’s method should show a significant increase in slope with no change in mean systemic pressure. These changes are exactly what we found and a preliminary report of this work has already been made (17). Clamping the aorta below the mesenteric veins causes just the opposite effect.

Alexander et al. (18) have showed that a sudden elevation of venous pressure brings about a very small, immediate increase in volume in the splanchnic bed but that sustained elevation of venous pressure causes a significant degree of pooling. These studies were entirely different from those obtained on the hind limb of the dog, which according to Alexander (19), suggest that the venous system in this region serves as a network of pipes returning blood from the periphery to the heart.

We do not know if the short-time constant area is represented by the rest of the circulation, but we certainly assume that the muscle circulation must be part of the fast-time constant area. Traystman and Bromberger-Barnea (20) in our laboratory found that drainage from the coronary sinus at constant coronary flow could be fit by a single exponential over a range of a decade with a time constant of approximately 0.05 minutes, a figure very close to that of our fast-time constant area.

The analysis of the experimental data which showed that epinephrine caused vasoconstriction of the long-time constant compartment and tended to cause vasodilatation of the short-time constant compartment is compatible with the known effects of epinephrine causing splanchnic vasoconstriction and muscle vasodilatation.

**IMPLICATIONS**

This study strongly suggests that changes in the distribution of blood flow controlled through changes in arteriolar tone are of much greater significance than are changes in venous tone during steady-state increases in venous return in response to epinephrine administration. Indeed, without the change in distribution, there would be no increase in venous return under isovolumic conditions except at high right atrial pressures (Fig. 9). At constant blood flow and low right atrial pressure, there would be essentially no change in blood volume. Although the study clearly shows that the capacitance of the systemic vascular system is significantly decreased by the administration of epinephrine, the effects of the reduction in both compliance and unstressed volume are largely canceled by the increased venous resistance downstream from the compliant areas.

The change in the distribution of flow is largely caused by an increase in the arteriolar resistance of the long-time constant channel, but
there is also a mean decrease in the arteriolar resistance of the short-time constant channel, although this change is not statistically significant (Fig. 6).

If essentially the same effects can be achieved by changes in the distribution of blood flow with no changes in venous tone, what purpose is served by the variety of well-known pathways available to change venous tone? It seems entirely reasonable that quick changes in venous tone could play a very important role in countering sudden changes in the filling pressure of the right atrium brought about by respiratory and postural changes or changes related to myocardial failure. Figure 9 shows that if right atrial pressure had to be as high as 15 cm H2O for the heart to pump blood, there would have been no venous return, regardless of the distribution of flow, without an increase in venous tone. The effect of epinephrine on venous tone alone could have provided a significant output independent of its effect on flow distribution. Figure 11 suggests that changes in venous tone per se could be of great significance under conditions of hemorrhage when the blood volume is significantly lowered.

The two-compartment model suggests that significant changes in cardiac output can occur during exercise at constant right atrial pressure with no change in either venous tone or external pressure from exercising muscles. All that is necessary is that arteriolar resistance to exercising muscles decrease, assuming that the muscle circulation has a short time constant for venous drainage. If the time constant is very low, the arteriolar vasodilatation would not even be accompanied by a significant fall in arterial blood pressure. For instance, if the time constant of the fast compartment approached zero, the mean arterial blood pressure would be precisely controlled at a fixed level regardless of the degree of arteriolar vasodilatation, because the increase in blood flow would exactly compensate for the decrease in arteriolar resistance. The beauty of this system is that peripheral factors controlling venous return would only be limited by how low the resistance to flow in the muscles could fall.

The idea that the increase in cardiac output with muscular exercise is closely related to vasodilatation in the muscles with a fall in peripheral resistance has been emphasized previously (21, 22). It has been suggested that the mechanisms which control arterial blood pressure, such as the carotid sinus reflex, are responsible for the increased cardiac output in the presence of the locally determined decrease in resistance to flow through the muscles. The scheme we are suggesting does not require an independent control of arterial blood pressure as long as the time constant for drainage of the muscles is very small and the heart pumps enough to keep right atrial pressure close to zero. Furthermore, if the resistance were lowered in vascular beds with long time constants and if right atrial pressure were close to atmospheric pressure prior to the lowering of the resistance, the cardiac output would have to decrease regardless of how potent the reflex mechanisms were in terms of increased heart rate and myocardial contractility.

If the time constant of the muscle vascular bed were of some finite value or if the blood flow to some long-time constant areas increased (skin for temperature control?), there would have to be some arteriolar vasoconstriction in some of the long-time constant areas to maintain arterial blood pressure.

Guyton et al. (23) have suggested that mean systemic pressure does increase in exercise due to changes in the elastic properties and external pressure of the veins. Unquestionably, these factors play a role, but the significance of the two-compartment analysis is that they need not occur to develop any venous return which the heart is capable of pumping.

It seems likely that arteriolar vasodilatation of muscles is analogous to opening an arteriovenous fistula when the connection between artery and vein is made with stiff tubing. The two-compartment model predicts that opening such a fistula would lead to an increase in the slope of the venous return curve with no change in mean systemic pressure. Guyton and Sagawa (24) carried out such an experiment and found exactly that. The increase in the slope of the venous return curve is not due to the decrease in parallel resistance, as suggested by Guyton, but rather to the stiffness of the tube used for the arteriovenous fistula, causing it to have a short time constant. For instance, if the fistula had a very compliant area upstream from a resistance, the slope could have decreased even though the parallel resistance decreased.

If the time constant of the muscle circulation approaches zero for venous drainage, the peripheral factors determining venous return could
initiate large changes in cardiac output merely by controlling the arteriolar resistance to the short-time constant area. Such control could be achieved regardless of the time constant for the slowly draining area in parallel. Is there any advantage in having the time constant of the slowly draining area very large? The greater the time constant of the slow area, the more stable the system is in relation to changes in blood volume (Eq. 6). If there were no long-time constant areas, small changes in blood volume would have large effects on cardiac output.

The present study suggests that considerable caution should be exercised in interpreting two types of experiments. Studies of changes in tone in isolated venous systems cannot be used directly to predict the effect of these changes on venous return without information concerning the drainage characteristics of compliant regions. It is entirely possible for increases in tone to be overshadowed by increases in venous resistance. To study the effects on venous return, it is perhaps better to study the entire vascular system rather than an isolated system. Nevertheless, these studies too can be misinterpreted by assuming changes in venous capacitance where such changes are absent. For instance, attempts have been made to quantify the change in the capacitance of the peripheral vasculature by measuring the translocation of blood between the systemic circulation and an external reservoir in animals whose systemic circulation is completely isolated by an extracorporeal bypass. Rose et al. (25), Braunwald et al. (26), and Henney et al. (27), among others, have used this experimental approach to study the effect of different drugs and agents on the capacitance vessels of the peripheral circulation. Any shift in blood volume between the peripheral circulation and the reservoir was interpreted as a change in the capacitance of the veins. Yet these findings could be equally well explained by a change in the distribution of blood flow between compartments. Thus, a decrease in the capacitance of veins need not be associated with an increase in venous return at constant right atrial pressure, and a decrease in blood volume at constant venous return and right atrial pressure need not be associated with a decrease in venous capacitance.

Finally, the linear, two-compartment model presented offers the possibility of integrating a number of seemingly complicated concepts into a simple framework. If the model is oversimplified, new experiments suggested by the model will define the problems. The model appears to adequately account for the major peripheral effects of epinephrine.

References


Effect of Epinephrine on Pressure, Flow, and Volume Relationships in the Systemic Circulation of Dogs
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