left cardiac outputs:

$$Q_{\mathrm{R}} = K_{\mathrm{R}} P_{\mathrm{sv}} \tag{1.4.8}$$

$$Q_{\mathrm{L}} = K_{\mathrm{L}} P_{\mathrm{pv}}. \tag{1.4.9}$$

Throughout this section we have tacitly assumed that the pressure outside the heart is zero (atmospheric). If not, then the distending pressures during diastole are not simply P_{sv} and P_{pv} but $P_{\mathrm{sv}} - P_{\mathrm{thorax}}$ and $P_{\mathrm{pv}} - P_{\mathrm{thorax}}$, where P_{thorax} is the pressure in the chest. In fact, P_{thorax} is slightly negative (with respect to the atmosphere), and this contributes to increased cardiac output by increasing the end-diastolic volume V_{ED}. This effect was first noticed because it disappears when the chest is opened during surgery. In the model developed below, we assume for simplicity that $P_{\mathrm{thorax}} = 0$ so that we can use (1.4.8) and (1.4.9) without modification. Then, effects of $P_{\mathrm{thorax}} < 0$ are considered briefly in Exercises 1.8 through 1.9.

1.5 Mathematical Model of the Uncontrolled Circulation

In this section we put together the ideas that have been developed above to construct a mathematical model of the circulation. In the form that we first present it, the model lacks the control mechanisms that regulate the circulation and make it serve the needs of the body. In subsequent sections we will use this model in several ways:

1. to study the *self*-regulating properties of the circulation, independent of external control mechanisms;

2. to explain the need for external control mechanisms;

3. to serve as a foundation on which we can construct a simple model of the control of circulation.

Our model is defined by the following equations (see Figure 1.6): First, we have the equations of the right and left hearts:

$$Q_{\mathrm{R}} = K_{\mathrm{R}} P_{\mathrm{sv}}, \tag{1.5.1}$$

$$Q_{\mathrm{L}} = K_{\mathrm{L}} P_{\mathrm{pv}}. \tag{1.5.2}$$

Second, we make the assumption that the systemic and pulmonary arteries and veins are compliance vessels. For simplicity, we use (1.3.2) instead of

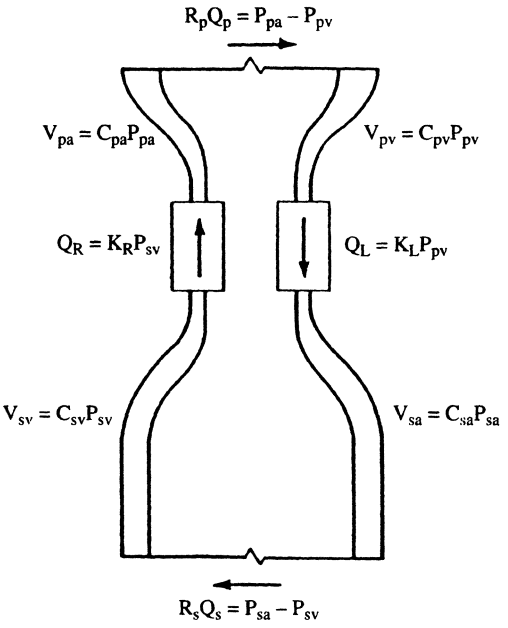

Figure 1.6. Equations of the circulation. One equation is shown for each of the eight principal elements of the circulation. For additional equations that relate these elements to each other, see the text. Each element is characterized by one parameter (K = pump coefficient, C = compliance, R = resistance) and two or three unknowns (Q = flow, P = pressure, V = volume). Subscript notation is s = systemic, p = pulmonary, a = arterial, v = venous, L = left, R = right.

(1.3.3). That is, we neglect V_d in these vessels. This gives the equations

$$V_{sa} = C_{sa}P_{sa}, \tag{1.5.3}$$

$$V_{sv} = C_{sv}P_{sv}, \tag{1.5.4}$$

$$V_{pa} = C_{pa}P_{pa}, \tag{1.5.5}$$

$$V_{pv} = C_{pv}P_{pv}. \tag{1.5.6}$$

Third, we assume that the systemic and pulmonary tissues act like resistance vessels, so that

$$Q_s = \frac{1}{R_s}(P_{sa} - P_{sv}), \tag{1.5.7}$$

$$Q_p = \frac{1}{R_p}(P_{pa} - P_{pv}). \tag{1.5.8}$$

At this point, we have an equation for each element of the circulation. Each equation contains a *parameter* that characterizes that element. These

parameters are the pump coefficients K_R, K_L, the resistances R_s, R_p, and the compliances C_{sa}, C_{sv}, C_{pa}, and C_{pv}. Suppose we are given the values of these parameters. Can we use equations (1.5.1) through (1.5.8) to determine the flows, pressures, and volumes of the model circulation? The answer to this question is negative; we do not yet have enough equations to determine the 12 unknowns

$$Q_R, Q_L, Q_s, Q_p; P_{sa}, P_{sv}, P_{pa}, P_{pv}; V_{sa}, V_{sv}, V_{pa}, V_{pv}.$$

The missing equations refer not to any particular element but to the circulation as a whole and to the way that its elements are connected. (Try to discover the missing equations for yourself before reading further.)

First, it is reasonable to assume that the total blood volume V_0 is given. This gives the equation

$$V_{sa} + V_{sv} + V_{pa} + V_{pv} = V_0, \tag{1.5.9}$$

in which V_0 is an additional parameter.

Next, we assume that the circulation is in a *steady state*, so that the flow into each of the compliance vessels must equal the flow out (why?). It follows that $Q_R = Q_L = Q_s = Q_p$, so we can drop the subscripts and just refer to all of the flows as Q, the cardiac output.

With these additional assumptions, we have nine equations for the nine unknowns $Q, P_{sa}, P_{sv}, P_{pa}, P_{pv}, V_{sa}, V_{sv}, V_{pa}, V_{pv}$. The model is complete.

Our next task is to solve the equations of the model. That is, we want to express each of the unknowns in terms of the parameters. (Try this for yourself before reading further.) An efficient plan of attack is as follows: First, express all of the pressures in terms of the flow Q. Then use the compliance equations to get the volumes in terms of Q. Finally, substitute in the equation for the total blood volume and solve for Q. With Q known (in terms of parameters only) we can go back and express the pressures and then the volumes in terms of parameters.

Here are the details. From the pump equations, we get the venous pressures in terms of Q:

$$P_{sv} = \frac{Q}{K_R}, \tag{1.5.10}$$

$$P_{pv} = \frac{Q}{K_L}. \tag{1.5.11}$$

Substituting this result in the resistance equations, we get the arterial pressures in terms of Q:

$$P_{sa} = \frac{Q}{K_R} + R_s Q, \tag{1.5.12}$$

$$P_{pa} = \frac{Q}{K_L} + R_p Q. \tag{1.5.13}$$

Substituting all four pressures into the compliance equations, we obtain

$$V_{sv} = \frac{C_{sv}}{K_R} Q, \tag{1.5.14}$$

$$V_{pv} = \frac{C_{pv}}{K_L} Q, \tag{1.5.15}$$

$$V_{sa} = \left[\frac{C_{sa}}{K_R} + C_{sa}R_s\right] Q, \tag{1.5.16}$$

$$V_{pa} = \left[\frac{C_{pa}}{K_L} + C_{pa}R_p\right] Q. \tag{1.5.17}$$

To save writing, we introduce the following combinations of parameters

$$T_{sv} = C_{sv}/K_R, \tag{1.5.18}$$

$$T_{pv} = C_{pv}/K_L, \tag{1.5.19}$$

$$T_{sa} = (C_{sa}/K_R) + C_{sa}R_s, \tag{1.5.20}$$

$$T_{pa} = (C_{pa}/K_L) + C_{pa}R_p. \tag{1.5.21}$$

Then (1.5.14) through (1.5.17) can be summarized by the equations

$$V_i = T_i Q, \; i = \text{sv, pv, sa, pa.} \tag{1.5.22}$$

We are now ready to substitute these expressions in the equations for the total blood volume and solve for Q. We get

$$(T_{sa} + T_{sv} + T_{pa} + T_{pv})Q = V_0, \tag{1.5.23}$$

so

$$Q = \frac{V_0}{(T_{sa} + T_{sv} + T_{pa} + T_{pv})}. \tag{1.5.24}$$

The solution is completed using the equations $V_i = T_i Q$ and $P_i = V_i/C_i$. We get

$$V_i = \frac{T_i V_0}{(T_{sa} + T_{sv} + T_{pa} + T_{pv})}, \tag{1.5.25}$$

$$P_i = \frac{T_i V_0}{C_i(T_{sa} + T_{sv} + T_{pa} + T_{pv})}, \tag{1.5.26}$$

where i = sa, sv, pa, and pv. Thus, we have a formula for each unknown in terms of parameters only.

The quantitative use of these formulae depends on having numerical values for the parameters. In particular, we need *normal resting values* for the parameters so that we can use the model to predict the effects of parameter changes away from the normal resting state of the circulation. It is easy to determine the parameters from data such as are given in Table 1.1 and Section 1.2 because each equation of our model (1.5.5–1.5.9) contains exactly one of the parameters, so it can be written as a formula

Table 1.2. Normal Resting Parameters of the Model Circulation

	Systemic	**Pulmonary**
R:	$R_s = 17.5$	$R_p = 1.79$ mmHg/(liter/min)
C:	$C_{sa} = 0.01$	$C_{pa} = 0.00667$ liters/mmHg
	$C_{sv} = 1.75$	$C_{pv} = 0.08$ liters/mmHg
	Right	**Left**
K:	$K_R = 2.8$	$K_L = 1.12$ (liters/min)/mmHg
V:	$V_0 = 5.0$ liters	

for that parameter in terms of the observed pressures, volumes, and flows. The results of this procedure are summarized in Table 1.2.

The procedure that we have just used for *identification* of parameters is based on the assumption that the model is correct. If we improve the model, then the best choice of parameters may change. An example of this is studied in Exercises 1.7 and 1.17.

1.6 Balancing the Two Sides of the Heart and the Two Circulations

The reader has probably noticed that most of the equations of the previous section came in pairs. The reason for this is the symmetry of form between the right and left heart and the systemic and pulmonary circulations. In fact, we can obtain one member of a pair from the other by making the subscript interchanges s $\leftrightarrow$ p and R $\leftrightarrow$ L (try it and see!). In the few equations that stand alone (because they refer to the circulation as a whole) these interchanges give us back the same equation as before.

If the corresponding parameters were quantitatively equal (that is, if we had $K_R = K_L, R_s = R_p$, etc.), then the two circulations would be quantitatively symmetrical with $P_{sa} = P_{pa}$, and so on. A glance at Tables 1.1 and 1.2 shows that this is far from being the case.

This raises the question of how the two sides of the heart and the two circulations are coordinated. What keeps the outputs of the right and left hearts equal? What mechanisms control the partition of blood volume between the systemic and pulmonary circulations? These are vital (and closely related) questions. If the left output exceeded the right output by only 10% for 1 minute, this would be enough to empty the vessels of the pulmonary circulation.

In our steady–state model of the circulation, the right and left cardiac outputs are equal by definition. In a time-dependent version of the model, we could see how this equality of output is maintained. Suppose, for ex-

ample, that K_R is suddenly reduced. Temporarily, Q_R will be less than Q_L, so there will be a net transfer of blood volume away from the pulmonary circulation and into the systemic circulation. This will raise the systemic venous pressure and lower the pulmonary venous pressure. The effect of these pressure changes will be to drive the cardiac outputs back toward equality. A net rate of transfer of volume will persist until equality of output of the two sides has been restored. Then a new equilibrium is established with a different partition of the blood volume than before.

In the steady-state model, we compute only the end result of this process. Using (1.5.25) and (1.5.18) through (1.5.21), we see that

$$\begin{aligned} \frac{V_p}{V_s} &= \frac{V_{pa} + V_{pv}}{V_{sa} + V_{sv}} \\ &= \frac{T_{pa} + T_{pv}}{T_{sa} + T_{sv}} \\ &= \left(\frac{C_{pa} + C_{pv}}{K_L} + C_{pa} R_p \right) / \left(\frac{C_{sa} + C_{sv}}{K_R} + C_{sa} R_s \right), \end{aligned} \tag{1.6.1}$$

where V_p is the total pulmonary volume and V_s is the total systemic volume. Thus, the partition of the blood volume between the two circulations is determined by the parameters, and a change in parameters that temporarily produces a disparity in output between the two sides of the heart eventually results in a volume shift that compensates for the parameter change and restores the equality of output.

The key to the success of this intrinsic control mechanism is the dependence of *cardiac output* on *venous pressure*. Suppose instead that the cardiac outputs of the two sides of the heart were given and equal. In that case Q would be a parameter and we would have to drop equations (1.5.1) and (1.5.2). We would have lost two equations but only one unknown, so we would be free to specify one more relationship. In fact, we could then assume that the pulmonary and systemic volumes (V_p, V_s) were separately given. This would lead to the equations

$$V_{sa} + V_{sv} = V_s, \tag{1.6.2}$$

$$V_{pa} + V_{pv} = V_p, \tag{1.6.3}$$

which would replace (1.5.9), increasing the number of equations by one. Thus, we would have the eight equations (1.5.3) through (1.5.8) and (1.6.2) and (1.6.3) for the eight unknowns (V_i, P_i) with Q as a new parameter. With these assumptions the pulmonary and systemic volumes would be arbitrary; there would be no mechanism available to hold them in a reasonable relationship to each other. These considerations show the importance of the dependence of cardiac output on venous pressure, not only for maintaining a balance between the two sides of the heart, but also for establishing a controlled partition of the blood volume between the pulmonary and systemic circulations.

1.7 The Need for External Circulatory Control Mechanisms

The arterioles in an exercising muscle dilate, and the systemic resistance R_s falls. The cardiac output rises, and the systemic arterial pressure is maintained. The increase in cardiac output comes primarily from an increase in heart rate while stroke volume remains fairly constant.

In this section we study the consequences of a change in R_s in our model of the *uncontrolled* circulation. We shall find a predicted response that is very different from the observed response described above. In the uncontrolled circulation a decrease in R_s results in only a modest increase in cardiac output. The most noticeable effect is a substantial fall in systemic arterial pressure. This shows the need for the external circulatory control mechanisms that are outlined in the next section.

We begin with an obvious but important remark. The effects of a change in R_s cannot be predicted solely from the equation of the systemic resistance, even though that is the only equation where R_s appears. If we neglect P_{sv} in equation (1.5.7) (an excellent approximation because P_{sv} is about 2 mmHg, whereas P_{sa} is about 100 mmHg), we get $P_{sa} = QR_s$. From this we might conclude that P_{sa} is proportional to R_s with Q constant or that Q is inversely proportional to R_s with P_{sa} constant. Neither conclusion is correct, since both P_{sa} and Q vary when R_s changes. The actual effects on P_{sa} and Q cannot be predicted without taking all of the other equations into account. That is the essence of a system of *simultaneous* equations.

In fact, we have already taken these equations into account when we solved for the unknowns in terms of the parameters. The formulae that we need are

$$Q = \frac{V_0}{T_{sa} + T_{sv} + T_{pa} + T_{pv}} \tag{1.7.1}$$

and

$$P_{sa} = \frac{V_0}{C_{sa}} \frac{T_{sa}}{T_{sa} + T_{sv} + T_{pa} + T_{pv}}, \tag{1.7.2}$$

where T_{sa}, etc., are given by (1.5.18) through (1.5.21).

Using these formulae and the parameter values given in Table 1.2, we can find the effects on Q and P_{sa} of reducing R_s to 50% of its normal value (while leaving the other parameters unchanged). The results are summarized in Table 1.3.

Note that the increase in cardiac output was only about 10% whereas the drop in arterial pressure was about 40%. This mechanism of adjusting the cardiac output is definitely inadequate to sustain reasonable levels of exercise, where cardiac output must be doubled or even tripled and where blood supply to nonmuscular tissue must be maintained.

Table 1.3. Effect of Changing Systemic Resistance on Cardiac Output and Systemic Arterial Pressure in the Uncontrolled Circulation

	Normal	$R_s = R_s^{\text{normal}}/2$	**Change**	**% Change**
Q	5.6	6.2	+0.6 liters/min	+11%
P_{sa}	100.0	57	−43.0 mmHg	−43%

The results that we have just derived can be summarized using the concept of sensitivity. If Y depends on X, and X changes, then the sensitivity of Y to X is defined to be

$$\begin{aligned} \sigma_{YX} &= \frac{\Delta \log Y}{\Delta \log X} = \frac{\log Y' - \log Y}{\log X' - \log X} \\ &= \frac{\log(Y'/Y)}{\log(X'/X)}, \end{aligned} \tag{1.7.3}$$

where $X' = X + \Delta X$ and Y' is the value that Y takes on when X is changed to X'. Note that the sensitivity is not influenced by a change of units in X or Y. It also makes no difference what base is used for the logarithms in these formulae. When the changes in X and Y are small, we have approximately

$$\sigma_{YX} = \frac{dY}{Y} \Big/ \frac{dX}{X}, \tag{1.7.4}$$

which shows that the sensitivity is roughly the ratio of relative (or %) changes. If $Y = aX^n$, then $\log Y = n \log X$ and $\sigma_{YX} = n$. In particular, if Y is proportional to X, then $\sigma_{YX} = 1$. If Y is inversely proportional to X, then $\sigma_{YX} = -1$.

From the numbers in Table 1.3, we conclude that $\sigma_{QR_s} = -0.15$, while $\sigma_{P_{sa}R_s} = +0.81$. It is not a coincidence that

$$-(\sigma_{QR_s}) + \sigma_{P_{sa}R_s} \approx 1. \tag{1.7.5}$$

This follows from the fact that $P_{sa} \approx QR_s$ as the reader can show by taking logarithms and applying the definition of sensitivity. Because of (1.7.5), we cannot increase the magnitude of the sensitivity of cardiac output to systemic resistance without *decreasing* the sensitivity of systemic arterial pressure to systemic resistance. Any mechanism that accomplishes one will automatically accomplish the other.

1.8 Neural Control: The Baroreceptor Loop

From the results of the previous section, it appears that it would be a good idea to hold P_{sa} constant. In that case, we should have $\sigma_{P_{sa}R_s} = 0$ and $\sigma_{QR_s} = -1$, which would be a tremendous improvement from the

standpoint of the circulatory response to exercise. The improvement would be twofold. First, $\sigma_{QR_s} = -1$ would mean that the cardiac output would double every time the systemic resistance were halved. Second, $\sigma_{P_{sa}R_s} = 0$ would mean that the systemic arterial pressure (and hence the blood flow to the nonexercising tissues and organs) would be maintained.

In the body, P_{sa} is controlled by a feedback mechanism called the baroreceptor loop (see Figure 1.7, in which an arrow indicates a positive, or excitatory, influence, and a bar indicates a negative, or inhibitory, influence). The elements of the baroreceptor loop are as follows:

1. The *baroreceptors* (B) are stretch receptors located in the carotid arteries and in the arch of the aorta. The baroreceptors transmit nerve

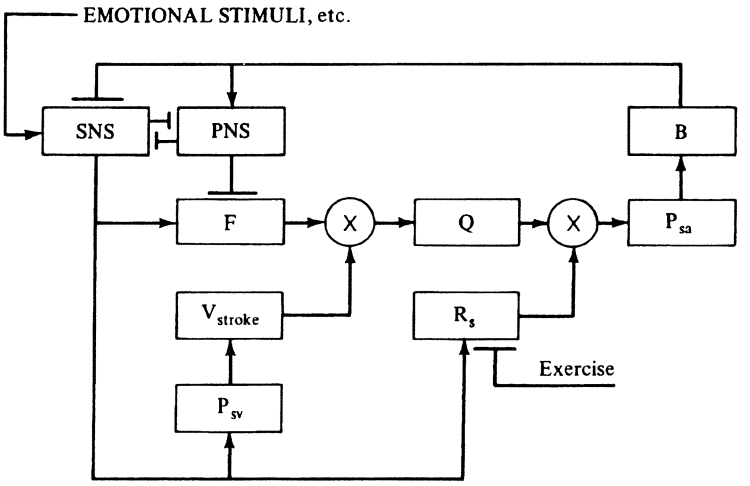

Figure 1.7. The baroreceptor loop. This diagram depicts the qualitative relationships among the many factors that regulate systemic arterial blood pressure. Arrowheads indicate positive influences, whereas bars indicate negative influences. The symbol × indicates multiplication. SNS = activity of the sympathetic nervous system, which increases the heart rate (F), the systemic venous pressure (P_{sv}), and the systemic resistance (R_s); PNS = activity of the parasympathetic nervous system, which slows the heart; B = activity of the baroreceptors, which stimulates the parasympathetic nervous system and inhibits the sympathetic nervous system. (Note that these two arms of the autonomic nervous system also inhibit each other.) V_{stroke} is the stroke volume, Q is the cardiac output, and P_{sa} is the arterial blood pressure. Note that any path through this diagram from P_{sa} back to itself involves an odd number of inhibitory influences. Thus, the whole system is a negative feedback loop (actually, several negative feedback loops working in parallel) that tends to stabilize the arterial blood pressure against changes such as emotional stimuli or exercise, which are shown here as inputs to the system.

impulses to the brain stem at a rate that increases with increasing arterial pressure (see Chapter 6).

2. The *parasympathetic nervous system* (PNS) is excited by activity of the baroreceptors. Its effect is to slow the heart rate (F).

3. The *sympathetic nervous system* (SNS) is inhibited by activity of the baroreceptors. It has several effects on the circulation, including:

   (a) increased heart rate;
   (b) increased venous pressure, and so increased stroke volume;
   (c) increased systemic resistance.

The loop is closed through the mechanics of the circulation, which implies that $Q = FV_{\text{stroke}}$ and that $P_{\text{sa}} = QR_{\text{s}}$.

Tracing any closed loop from P_{sa} back to P_{sa} in Figure 1.7, we find an odd number of inhibitory influences. This means that any changes in P_{sa} lead to *compensatory* changes through the baroreceptor loop.

We will not present a detailed model of the baroreceptor loop here (see Chapter 6, for some further discussion). Instead, we model its overall function by assuming that the baroreceptor loop adjusts the heart rate F until the systemic arterial pressure achieves a target value P^*. Note that this model ignores the effects of the sympathetic nervous system on venous pressure and on systemic resistance. These effects are less important than the effect on heart rate in the normal operation of the circulation.

Thus, we have a new unknown, F, that was previously a parameter and a new parameter, $P_{\text{sa}} = P^*$, that was previously an unknown. Also, because F is no longer a parameter, we have to rewrite (1.5.1) and (1.5.2) in the form

$$Q_{\text{R}} = FC_{\text{R}}P_{\text{sv}}, \tag{1.8.1}$$

$$Q_{\text{L}} = FC_{\text{L}}P_{\text{pv}}, \tag{1.8.2}$$

where C_{R} and C_{L} are the *diastolic compliance* of the right and left hearts (see Section 1.4), so that $C_{\text{R}}P_{\text{sv}}$ is the right stroke volume and $C_{\text{L}}P_{\text{pv}}$ is the left stroke volume.

This gives us a model of the controlled circulation in which the equations are (1.8.1) and (1.8.2) together with (1.5.3) through (1.5.9) and the steady-state relation $Q_{\text{R}} = Q_{\text{p}} = Q_{\text{s}} = Q_{\text{L}}$. The unknowns are the same as before except that now F replaces P_{sa}.

Instead of solving these equations directly, we make some approximations. First, we neglect P_{sv} compared to P_{sa} in the equation of the systemic resistance. This represents a 2% error, and it gives us the equation

$$QR_{\text{s}} = P^*. \tag{1.8.3}$$

Next, we neglect the pulmonary volumes in comparison with the systemic volumes in the equation of the total blood volume. This represents a 10%

error, and it gives us

$$V_{sa} + V_{sv} = V_0, \tag{1.8.4}$$

which can be rewritten as

$$C_{sa}P^* + C_{sv}P_{sv} = V_0. \tag{1.8.5}$$

We can now determine Q directly from (1.8.3) and P_{sv} directly from (1.8.5):

$$Q = \frac{P^*}{R_s}, \tag{1.8.6}$$

$$P_{sv} = \frac{V_0 - C_{sa}P^*}{C_{sv}}. \tag{1.8.7}$$

Substituting these results in the equation of the right heart (1.8.1), we can solve for the heart rate

$$F = \frac{P^*C_{sv}}{R_sC_R(V_0 - C_{sa}P^*)}. \tag{1.8.8}$$

These results summarize the performance of the controlled circulation. We have achieved what we set out to do: Since $P_{sa} = P^*$, which is constant, $\sigma_{P_{sa}R_s} = 0$. Again, since P^* is constant, $\sigma_{QR_s} = -1$.

Thus, our model of the controlled circulation responds to changes in R_s with (inversely) proportional changes in cardiac output while the arterial pressure is maintained. In the model as in life, the mechanism responsible for the increased cardiac output is an increase in heart rate, since the venous pressure and stroke volume ($V_{stroke} = C_RP_{sv}$) are independent of R_s in the model.

In the uncontrolled circulation the cardiac output depends on all of the parameters of the model; in the controlled circulation it depends only on P^* and R_s. This isolation of cardiac output from extraneous influences is just as important as the heightened sensitivity to R_s. We give one example. In the uncontrolled circulation, we had $\sigma_{QV_0} = 1$, which means that the cardiac output is proportional to the blood volume (see equation 1.5.24). In the controlled circulation, $\sigma_{QV_0} = 0$, which means that the cardiac output is protected against blood loss, for example. From (1.8.8), we see that the mechanism of adaptation to blood loss is an increase in heart rate that compensates for the decrease in stroke volume. We also see that the model breaks down when $V_0 = C_{sa}P^*$, which corresponds to complete depletion of the systemic venous blood.

We have shown that the response of the controlled circulation to stress is very different from that of the uncontrolled circulation. It is remarkable that such dramatic changes in behavior emerge when the only change in the mathematical model is to make one parameter into an unknown and one unknown into a parameter.

1.9 Autoregulation

Up to this point, we have treated the systemic resistance as a parameter. In this section we shall consider the local control of systemic resistance. Central control of systemic resistance was mentioned, but not modeled, in the previous section (see also Chapter 6).

There are two phenomena that come under the term autoregulation:

1. When the pressure–flow relation of a tissue is measured, it often turns out that there is a range of pressures in which the flow is relatively insensitive to the pressure difference.

2. At constant pressure difference, the flow through many tissues depends on the rate of O_2 consumption of the tissue.

In the normal function of the circulation, the second phenomenon is more important than the first, since the pressure difference is relatively constant, as we have just seen in the previous section. In pathological conditions, the first phenomenon may be important for regulating blood flow in the face of fluctuating pressures.

In this section we outline a simple model that accounts for both phenomena through a single mechanism. The model that we shall describe is a simplified version of a model proposed by Huntsman, Attinger, and Noordergraaf.

The key hypothesis is that the resistance of a tissue is regulated by the venous O_2 concentration of the tissue. In general, *concentration* means the amount per unit volume, and its units depend on how the amount is measured. In the case of a gas, it is convenient to measure the amount of gas in terms of the volume that the gas would occupy under some specified conditions of temperature and pressure. In physiology, the most natural conditions are atmospheric pressure and body temperature. When this is done, the concentration becomes dimensionless (volume/volume.)

For example, the concentration of O_2 in blood, denoted by $[O_2]$, is the number of liters of O_2 that are carried in one liter of blood. Oxygen is carried in blood bound to hemoglobin, and when all of the O_2–carrying sites in the hemoglobin molecules are occupied, the concentration of O_2 in blood is $\frac{1}{5}$. Coincidentally, this is the same as the concentration of O_2 in the atmosphere itself. Under normal conditions, the hemoglobin becomes saturated as it passes through the lungs, so that the arterial concentration $[O_2]_a = \frac{1}{5}$. The O_2 concentration of arterial blood is constant for all of the tissues of the body, but it may vary under conditions of high altitude or anemia. In the former case, the hemoglobin may fail to be saturated in the lung. In the latter case, the concentration of hemoglobin in blood is lower than normal. In both cases, $[O_2]_a$ is reduced, but this reduction is felt by all tissues of the body.

The venous O_2 concentration, $[O_2]_v$, is different in the different tissues of the body. Let M (metabolic rate) stand for the rate of O_2 consumption of a tissue (M has units of liters/minute). Also, let Q be the blood flow to the tissue in question. The rate at which O_2 is delivered to the tissue in the arterial blood is $Q[O_2]_a$, the units of which are (liters of blood/minute) $\times$ (liters of O_2/liter of blood). Similarly, the rate at which O_2 leaves the tissue in its venous blood is $Q[O_2]_v$. If the tissue is in a steady state, the difference must be accounted for by the metabolic rate of the tissue. This gives the equation

$$Q[O_2]_a - Q[O_2]_v = M, \tag{1.9.1}$$

which is called *Fick's principle.* Thus,

$$[O_2]_v = [O_2]_a - M/Q. \tag{1.9.2}$$

This formula shows that $[O_2]_v$ may serve as an index of the adequacy of the blood supply in relation to the metabolic rate of the tissues. When the blood supply is just barely sufficient to sustain the metabolic rate, then

$$Q = Q^* = M/[O_2]_a \quad \text{(this defines } Q^*\text{)}, \tag{1.9.3}$$

and we get $[O_2]_v = 0$. As Q is raised above Q^*, $[O_2]_v$ rises, and finally, $[O_2]_v \to [O_2]_a$ as $Q \to \infty$. This shows why it might be reasonable to use $[O_2]_v$ to regulate the resistance of a tissue to blood flow.

A problem with this hypothesis is that resistance is regulated on the arterial side of the tissue, not on the venous side. The venous O_2 concentration is determined by the *tissue* O_2 concentration, however, and the arterioles run through the tissue and may therefore be influenced by the tissue O_2 concentration.

Suppose, for example, that

$$R = R_0[O_2]_v, \tag{1.9.4}$$

where

$$R = P/Q \tag{1.9.5}$$

is the resistance of the tissue to blood flow, P is the arteriovenous pressure difference ($P = P_{sa} - P_{sv}$), and R_0 is the constant of proportionality that relates the resistance of the tissue to the venous O_2 concentration.

Equation (1.9.4) simply asserts that tissue resistance to blood flow is proportional to venous O_2 concentration. This is the simplest of a class of models in which tissue resistance is regulated by venous O_2 concentration.

To study the consequences of this simple hypothesis, we substitute (1.9.2) and (1.9.5) into (1.9.4) to obtain the pressure–flow relation of a tissue in

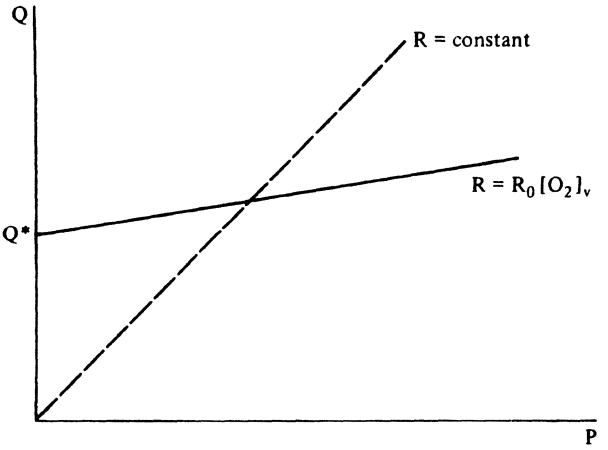

Figure 1.8. Pressure–flow relation of a tissue with and without autoregulation. $P = P_{sa} - P_{sv}$ = pressure difference driving flow through the tissue, and Q is the resulting flow. The dashed line shows the unregulated relationship characterized by a constant resistance R, and the solid line shows the autoregulated response, in which the resistance is proportional to the venous oxygen concentration $[O_2]_v$, with R_0 as the constant of proportionality. Note that the unregulated relationship includes the origin ($Q = 0$ when $P = 0$), but that in the autoregulated case there is still nonzero flow ($Q = Q^*$) even when ($P = 0$).

which resistance is regulated in this way. The result is

$$Q = \frac{M}{[O_2]_a} + \frac{P}{R_0[O_2]_a} \tag{1.9.6}$$

$$= Q^* + \frac{P}{R_0[O_2]_a}, \tag{1.9.7}$$

where $Q^* = M/[O_2]_a$. This result is plotted in Figure 1.8.

The behavior of the model tissue is summarized by the following statements, which the reader should be able to verify:

1. The sensitivity of flow to pressure (σ_{QP}) is less when $R = R_0[O_2]_v$ than when R = constant.

2. The tissue always receives at least the minimum flow Q^* required to sustain its metabolic rate. (Think about how this works. When $P \to 0$, why doesn't $Q \to 0$ in the model? What happens to R and $[O_2]_v$?)

3. At constant P, if M changes, then $\Delta Q = \Delta Q^* = \Delta M/[O_2]_a$. This means that the change in blood flow is just what is needed to support the extra O_2 consumption.

4. At constant P, if M increases, then R automatically decreases. (Plot R as a function of M with $P, [O_2]_a$, and R_0 constant.)

5. If $[O_2]_a$ changes (with P and R_0 constant), then Q automatically adjusts in such a way that $Q[O_2]_a = \text{constant}$. Therefore, the rate of O_2 supply to all of the tissues is the same as it was before the change in $[O_2]_a$.

In summary, the simple device of setting $R = R_0[O_2]_v$ (instead of $R =$ constant) makes the blood supply to a tissue less sensitive to pressure changes and more responsive to the needs of the tissue.

1.10 Changes in the Circulation Occurring at Birth

The circulation forms a simple loop after birth. Before birth, however, the configuration of the circulation is complicated by additional connections. One of these is a vessel called the *ductus arteriosus*, which connects the pulmonary and systemic arteries near the heart. Another is an opening in the wall that separates the right and left atria. This opening, called the *foramen ovale*, is guarded by a flap of tissue that acts as a valve to ensure that blood flow through the foramen always goes from right to left.

The function of these extra connections is to shunt blood away from the lungs, which are collapsed before birth and which therefore present high resistance to blood flow.

In this section we present a simple model of the *fetal circulation* (the circulation before birth), and we shall use this model to explain the sequence of changes (initiated by the first breath) that close the shunts and establish the single-loop configuration of the circulation that persists into adult life.

The model is shown in Figure 1.9. The shunt flows are the ductus flow Q_d and the foramen flow Q_f. If these are both zero, then the model takes on the configuration of a simple loop in which blood flows through the right heart; the pulmonary arteries, tissues, and veins; the left heart; and the systemic arteries, tissues, and veins.

Note that the flow through the ductus arteriosus is not always in the direction indicated by the arrow in Figure 1.9. The arrow points in the direction of the flow that we have chosen to call positive, which is also the normal direction of flow during fetal life. After birth but before the closure of the ductus arteriosus, however, the flow through the ductus is in the opposite direction. The reasons for this sudden reversal at birth will be explained below. The two situations are easily accommodated by a single system of equations if we consider the reverse flow through the ductus as being negative. Thus, $Q_d > 0$ means that the flow is in the direction defined by the arrow in Figure 1.9, whereas $Q_d < 0$ means that flow is in the opposite direction.