General Principles

Aims of the control system

(1) Flow: To supply cardiac output in accord with aggregate demand for blood from the whole body, and to distribute this cardiac output to the various tissues at constant pressure in proportion to their local demand.

(2) Pressure: To hold arterial pressure constant and the venous pressure down near zero.

(3) Balance: To achieve the foregoing while maintaining the equality of output between the right and left sides of the heart and a relatively fixed partition of blood volume between the systemic and pulmonary vascular beds.

Comments and Definitions

(1) Cardiac output: The volume of blood pumped by either side of the heart per unit time. Since the heart pumps in distinct beats

$$\begin{aligned}\text{Cardiac output} &= (\text{Stroke volume}).\ (\text{Heart Rate}) \\ &= (70\ \text{ml.}).\ (80\ \text{beats/min.}) \\ &= 5600\ \text{ml./min.}\end{aligned}$$

Cardiac output is not constant but may rise by a factor of 3 or more during exercise.

(2) "Demand" There is an important relation between the blood flow to a tissue, the rate of production or consumption of some material in the tissue, and the concentrations of that substance

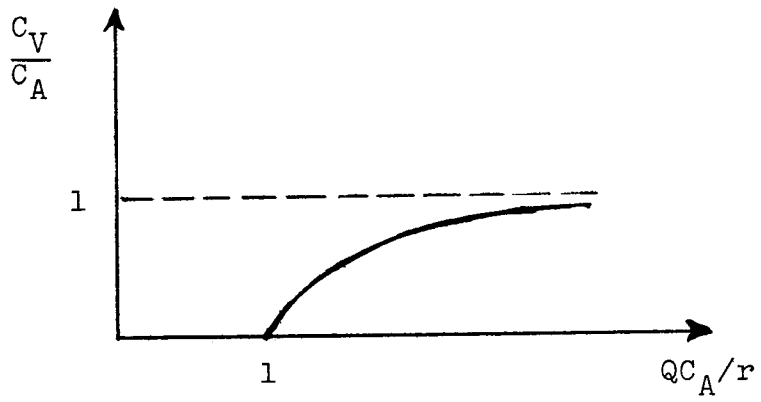
in the arterial and venous blood. Physiologists call this the Fick Principle. For example, let r be the rate of consumption of oxygen by the tissue, C_A = arterial oxygen concentration, C_V = venous oxygen concentration, Q = blood flow. Then

$$r = Q(C_A - C_V) \quad .$$

A useful form of this equation is

$$C_V = C_A - r/Q$$

because in the normal individual C_A is constant (arterial hemoglobin is nearly 100% saturated).



Demand is therefore the metabolic rate of a tissue, and the tissue announces how well its demands are satisfied by means of the concentration of oxygen (or other substances) in its venous blood.

(3) Pressure. Blood pressure is measured in mm Hg. Typical mean pressures are

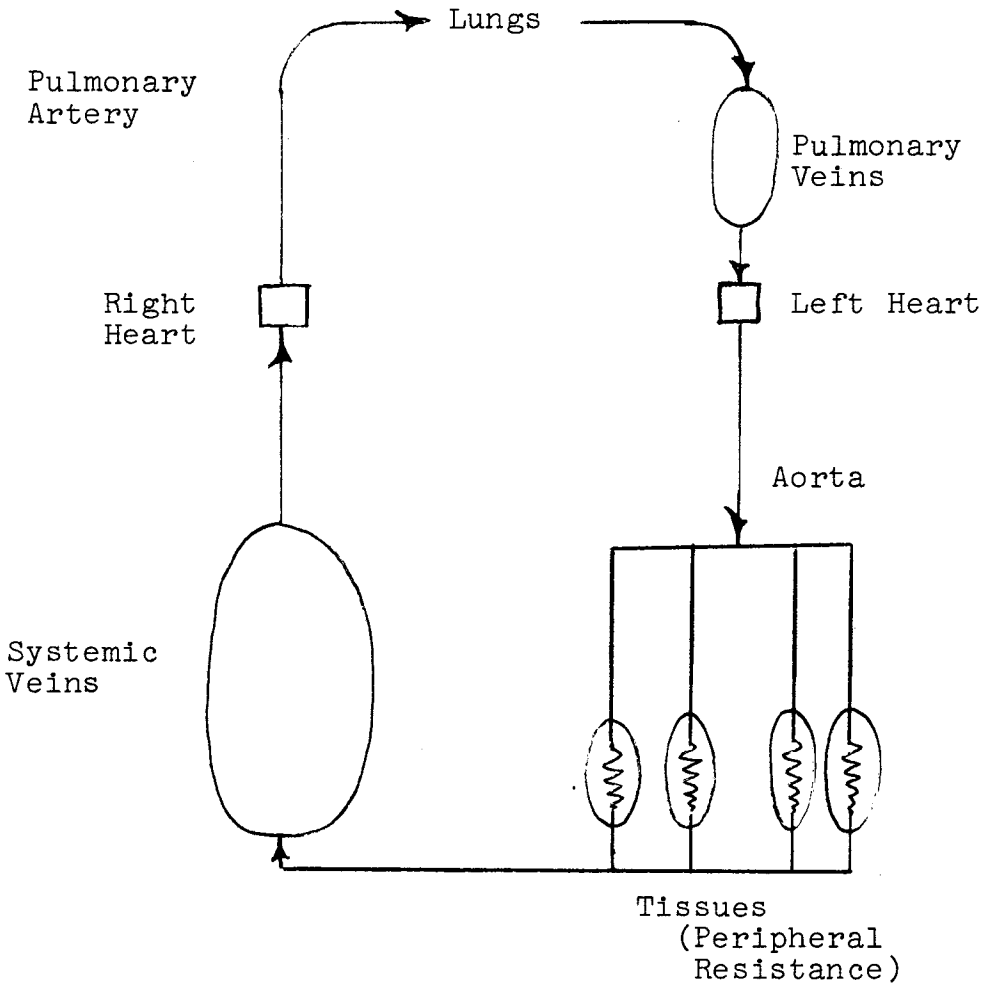
Aorta	100
Pulmonary Artery	15
Systemic Veins	2
Pulmonary Veins	5

(4) Resistance = the ratio of pressure difference to flow for a given vascular bed, and is controlled primarily by the diameters of the vessels on the input side of the bed (arterioles). Most vascular beds show non-linear pressure flow relations but much of this non-linearily can be understood in terms of the responsiveness of arteriolar diameter to the tissue concentrations of various substances and hence to flow. We shall therefore assume that for each vascular bed $P = QR$, but R may depend indirectly on flow, and also on nervous control.

(5) Blood volume and its distribution: At any instant the overwhelming fraction of the blood volume resides in the veins, and is distributed therefore between the systemic and pulmonary veins. The systemic venous bed in turn is much larger than the pulmonary, and holds a much larger volume of blood. Therefore, a shift of volume from the systemic circuit to the pulmonary that might be small from the standpoint of the systemic circuit could be catastrophic to the pulmonary circuit. Such shifts will occur whenever the outputs of the two sides of the heart

are unequal. Therefore there is an intimate connection between control of blood volume distribution and the control of the equality of output between the right and left hearts.

Diagram of the Circulation:



Elements of the control system:

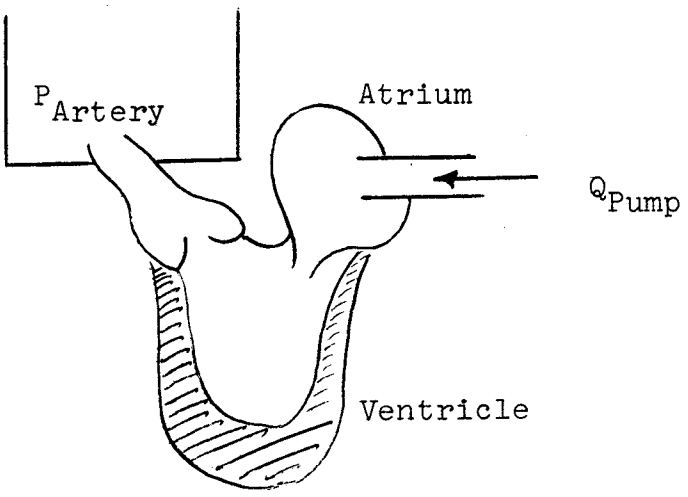
(1) The ventricle

Mechanical factors

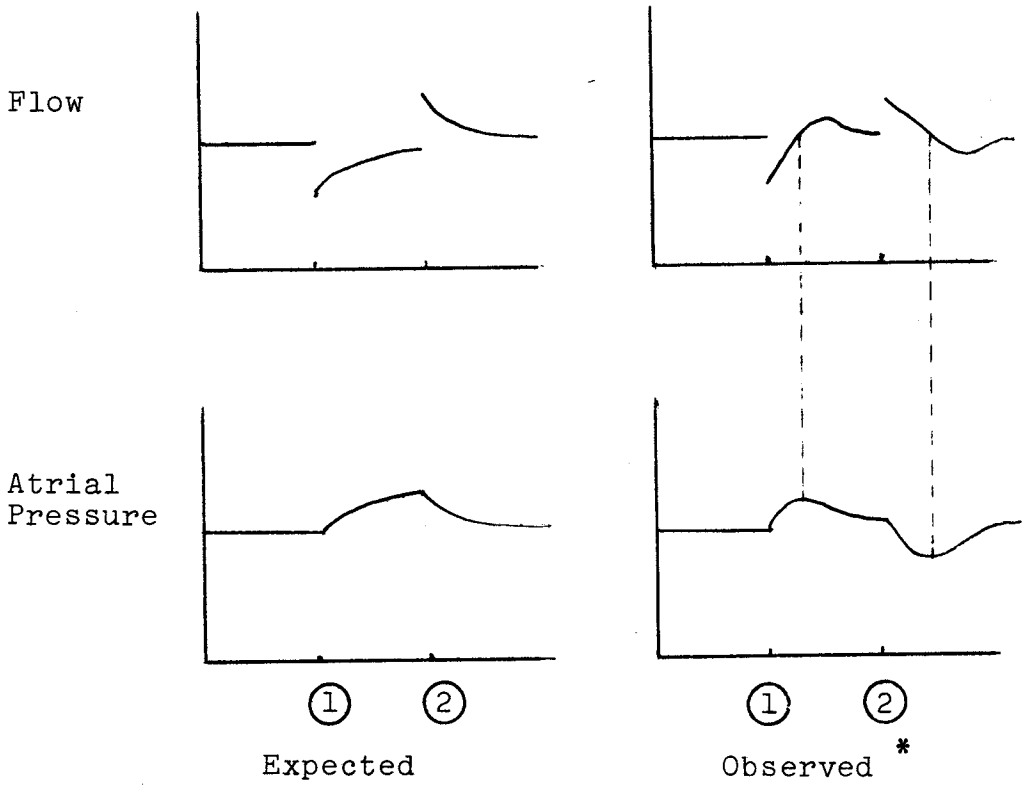
Atrial (venous) pressure: At constant heart rate, the volume of the ventricle prior to each beat is determined by the pressure in the upstream venous reservoir. This volume sets the initial fiber length for each contraction and hence the number of participating cross-bridges. The sensitivity to venous pressure is remarkable. Right heart output goes from 1 → 5 liters/min with a change of venous pressure of only 3 mm. Hg.

Arterial pressure: On the basis of muscle mechanics, one would expect decreased shortening, and hence decreased stroke volume with increased arterial pressure. However, such influences are slight in the steady state, though transient changes do occur. It appears that the ventricle adapts to the elevated pressure (mechanism unknown) so that it can pump the same flow at the same inflow pressure. Whatever sensitivity to arterial pressure does exist is minimized further by the arrangement of the two ventricles in series, see below.

Remark: Consider the following experiment. One side of the heart (atrium + ventricle) is supplied by a constant flow pump and the arterial pressure is controlled. After a control period the arterial pressure is abruptly raised. If the output of the ventricle falls transiently,



Step in Arterial Pressure
Applied at ①, Removed at ②



* (See footnote next page)

then the volume stored in the atrium necessarily rises because of the temporary inequality between the ventricle's output and the pump flow. When the atrial pressure becomes high enough, the ventricle is sufficiently stretched before each beat to pump the old flow against the elevated load. This reasoning leads to the predicted results drawn on the previous page (EXPECTED). The key point is that the atrial pressure remains high during the period that the load is elevated. But the observed* results show a fall in atrial pressure following the initial rise and suggesting that the ventricle has adapted to the new load in the sense that it can pump the same volume of blood against the new load at the old fiber length. Question: Is this adaptation dependent on an initial period of stretch?

Other factors:

Heart rate: First, recall that cardiac output = (stroke volume) × (heart rate). Also increased rate increases the strength of individual contractions by the Ca^{++} mechanism (see previous lecture). On the other hand, high rate can interfere with ventricular filling and reduce stroke volume. Heart rate is controlled at the sinoatrial node by the balance between two types of innervation:

Sympathetic	→ norepinephrine release at node	→ increased heart rate
Parasympathetic (vagus nerve)	→ acetyl choline release at node	→ decreased heart rate

*Sarnoff & Mitchel, Amer. J. Medicine 34,440,1963. Note: atrial pressure measured. Flow reconstructed here on the principle $C\left(\frac{dP}{dt}\right)_{atrium} = Q_{in} - Q_{out} = Q_{pump} - Q_{ventricle}$

Sympathetic innervation of the ventricle: Sympathetic nerve endings also release norepinephrine in ventricular muscle and this leads to increased strength of contraction and increased stroke volume at any given heart rate.

(2) The Heart-Lung as a system

Output of the left heart follows the output of the right because:

$$\left.\begin{aligned} C\,\frac{dP}{dt} &= Q_r - Q_L \\ Q_L &= KP \end{aligned}\right\} \rightarrow \frac{dQ_L}{dt} = \frac{K}{C}\,(Q_r - Q_L)$$

where

Q_r = right output

Q_L = left output

C = compliance of pulmonary veins

K = ratio of left heart output to pulmonary venous pressure.

Note that K/C has dimensions of time. Similar equations could be written down to show that the right heart follows the left, but the time constant would be much larger. Therefore it is appropriate to regard the right and left heart (and the intervening pulmonary circuit) as a single unit the output of which is controlled at the right heart. This has the effect of making cardiac output insensitive to systemic arterial pressure, independent of whether the left ventricle adapts to changes in systemic arterial pressure or not.

Note also that at equilibrium we have $Q_L = K_L P_L$, $Q_R = K_R P_R$, $Q_L = Q_R$ and hence $\frac{P_L}{R_R} = \frac{K_R}{K_L}$. Thus the ratio of the venous pressures is controlled by the ratio of the sensitivities of cardiac output to venous pressure of the two sides of the heart. If either ventricle becomes less sensitive to its upstream venous pressure, there is a shift in blood volume. For example stenosis (constriction) of the mitral valve (left heart inflow) makes the left ventricle less sensitive to pulmonary venous pressure and blood "backs up" in the pulmonary circuit.

(3) The peripheral resistance under metabolic and central control.*

As discussed above we expect the venous concentration of oxygen for a tissue to be given by

$$C_V = C_A - r/Q \quad .$$

If the venous blood is in equilibrium with the rest of the tissue, then the partial pressure of oxygen throughout the tissue will be some function of the venous oxygen concentration. As the walls of the arterioles pass through the tissue, it is possible to assume that the resistance to flow would be regulated by the venous oxygen concentration. The simplest possible assumption is $R = aC_V$, in which case we have

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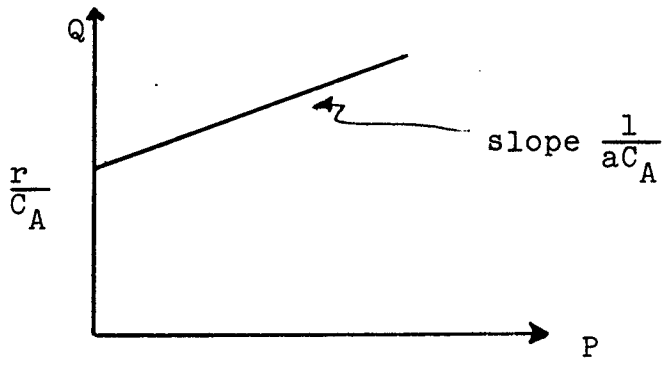
* For a more detailed analysis, see Huntsman, Attinger, and Noordergraaf, "Autoregulation of Peripheral Vascular Resistance: A Model", Proc. Ann. Conf. Engineering in Medicine and Biology. Houston 1968.

$$P = aC_V Q = a(C_A - \frac{r}{Q})Q = aC_A Q - ar$$

or

$$Q = \frac{P}{aC_A} + \frac{r}{C_A}$$



Remark: The foregoing is a steady-state pressure-flow relation. Since C_V will not change instantaneously, the instantaneous pressure-flow relation will always be a straight line through the origin. One can derive the equation for the dynamics of resistance changes as follows. Let $f(C_V)$ be the function giving the total oxygen content of the tissue at any instant. Then

$$\frac{d}{dt} f(C_V) = f'(C_V) \frac{dC_V}{dt} = Q(C_A - C_V) - r$$

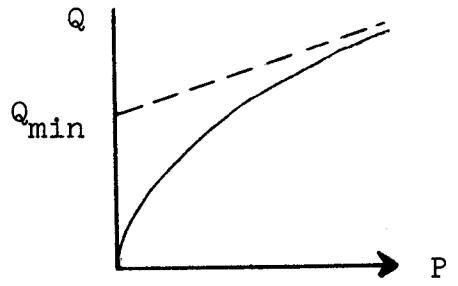
Multiplying through by a, we have

$$\frac{dR}{dt} = \frac{1}{f'(C_V)} [Q(aC_A - R) - ar]$$

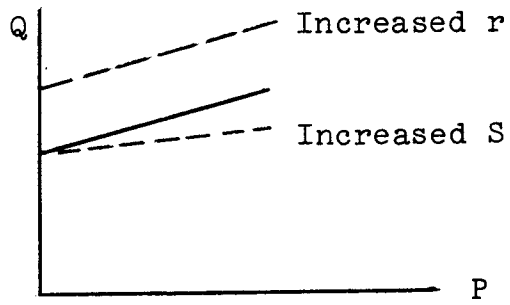
$$= \frac{1}{f'(C_V)} [P(\frac{aC_A}{R} - 1) - ar]$$

$$= \frac{1}{f'(C_V)} [\frac{PaC_A}{R} - (P + ar)]$$

Remark: In the foregoing picture it is assumed that the rate of consumption of oxygen r, is independent of the concentration of oxygen in the tissue. This is true (if at all) only at relatively high concentrations of oxygen; sufficiently high that the relevant enzymes are saturated. As the pressure falls and $Q \to Q_{min}$, $C_V \to 0$, which means that r will have to fall. The effect of this will be that a realistic pressure flow plot would look like this. One reason for maintaining blood pressure, then, is to keep the tissue oxygen high enough (by keeping the flow sufficiently above Q_{min}) that the supply of oxygen will not limit the work of the tissue.

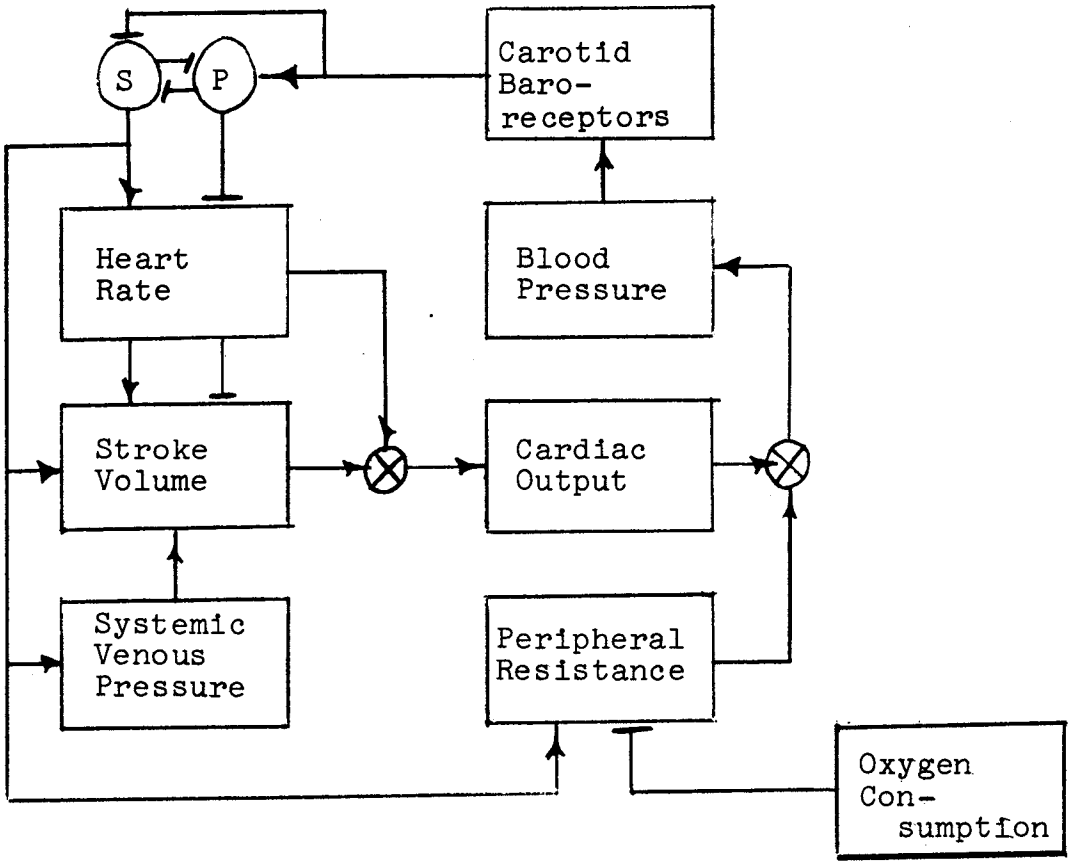


Central control of the peripheral resistance can be brought into the foregoing picture by assuming that the resistance is also proportional to "sympathetic tone", S (i.e., the frequency of impulse arriving via sympathetic nerves). That is, we write $a = a_o S$ or $R = a_o S C_V$. In that case the slope, but not the intercept, of the pressure-flow relation is under nervous control. This has the effect that each tissue can command at least a minimum flow according to its metabolic needs, but the excess above that is under central control.



(4) The baroreceptor loop

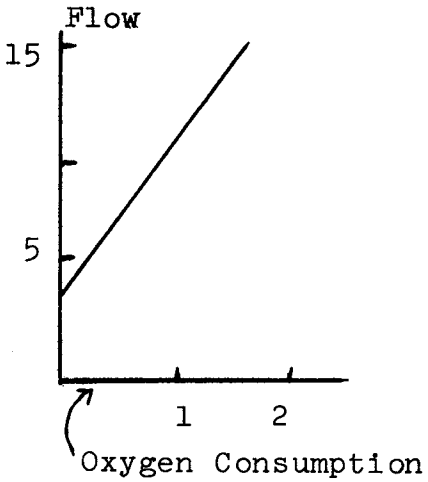
The carotid arteries have specialized receptors which sense arterial pressure and relay the information to the brain where it is used to control the balance between sympathetic and parasympathetic outflow:



Remark: The four modes of output of the sympathetic nervous system all act to support blood pressure. However, the first three modes (heart rate, stroke volume, systemic venous pressure) act on blood pressure only through an increase in cardiac output, while the fourth (peripheral resistance) does not act in this way. Therefore, the balance between the cardiac actions of the sympathetic nervous systems and its peripheral actions will determine how much increase in cardiac output (if any) will accompany a change in tissue metabolism.

Experiments and Models

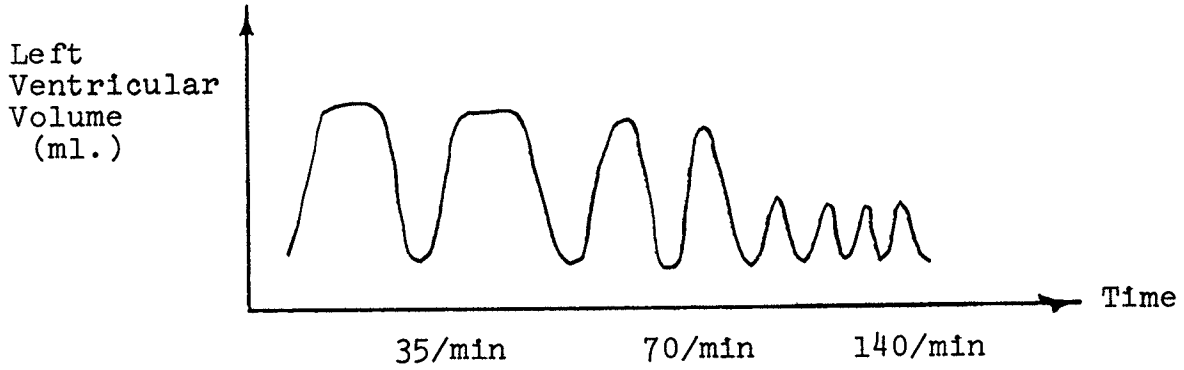
(1) Exercise:* During exercise sufficient to raise the heart rate from 60 → 180 beats/min., cardiac output varies linearly with heart rate (5 → 15 liters/min.) and stroke volume and mean blood pressure are nearly constant. The graph of cardiac output vs. oxygen consumption is linear with slope ∿ 6 but not through the origin. This slope compares favorably with the fact that at 100% saturation of hemoglobin with oxygen, 5 liters of blood are required to transport 1 liter of oxygen.



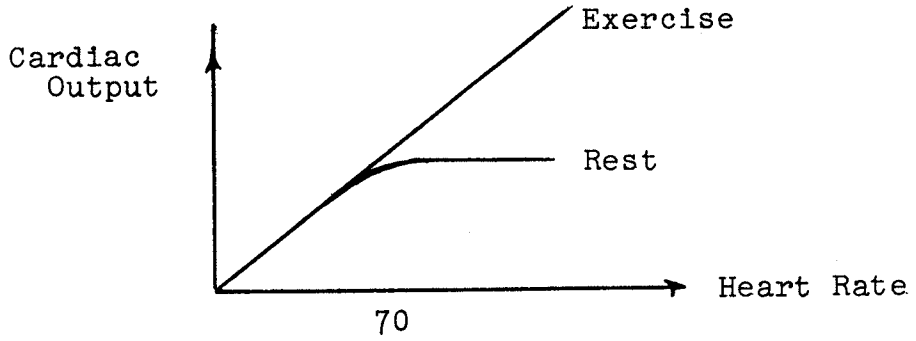
* Berne & Levy, Cardiovascular Physiology Mosby: St. Louis 1967, pp. 228-243.

(2) Heart rate and stroke volume with pacemaker*

Exercise studies in normal individuals suggest that cardiac output is proportional to heart rate. But suppose heart rate is artificially raised without a corresponding demand for blood from the tissues. Schematically the results are as follows:



At low rates, stroke volume is maintianed with increasing rates (so that cardiac output increases) but once the normal range of rates is reached, increased heart rate leads to a proportional decrease in stroke volume and no increase in cardiac output (in the absence of metabolic demand. We can summarize these results as follows



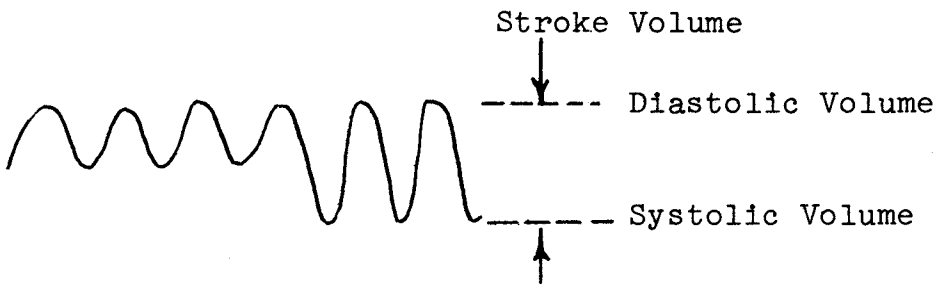
* Karloff, et. al.,"Adaptation of the left ventricle to sudden changes in heart rate in patients with artificial pacemakers", Cardiovascular Research 7, 322 (1973).

A further observation in the pacemaker patients is that the changes in stroke volume which compensate for changes in output at rates above about 70/min. are brought about by changes in the diastolic volume of the ventricle, the systolic volume remaining nearly unchanged. Moreover, the compensation occurs instantaneously and therefore is probably independent of neural mechanisms.

It is appropriate to remark here that during exercise, although stroke volume is maintained, heart size <u>decreases</u>. Thus the decrease in diastolic volume shown above apparently occurs, but is accompanied by a decrease in systolic volume, the latter decrease is probably a consequence of increased sympathetic tone.

It should also be noted that pacemaker patients can exercise at <u>fixed</u> heart rate with relatively normal increases in cardiac output, but these increases are achieved through stroke volume changes. Presumably, on the basis of the foregoing, diastolic volume is relatively constant while systolic volume decreases as a consequence of increased sympathetic tone.

Predicted response of ventricular volume to exercise at fixed heart rate:



(3) Cardiac output and peripheral resistance*

In these experiments a dog was exercised on a treadmill and the following quantities were measured: Cardiac Output, Heart Rate, Stroke Volume, Mean Arterial Pressure, and Peripheral Resistance. Changes similar to those described under exercise were obtained. Then the same exercise was performed with feedback control of peripheral resistance. This was accomplished by means of an inflatable cuff surrounding the abdominal aorta. Compression of the cuff was controlled by the measured pressure and flow so that the ratio of these quantities was always constant. In this situation the large changes in heart rate and cardiac output that occur at the onset of exercise were essentially abolished, although a slower change remained reaching only about a 30% increase and paralleling the small increase in pressure that occured with or without the control of resistance. With peripheral resistance controlled the dog could not continue exercising for any extended time.

Note: For further information on control of the heart during exercise consult the following articles in Physiological Reviews

1974 v. 54 L.B. Rowell "Human Cardiovascular Adjustments to Exercise and Thermal Stress".

1971 v. 51 P.I. Korner "Integrated Neural Control of the Circulation"

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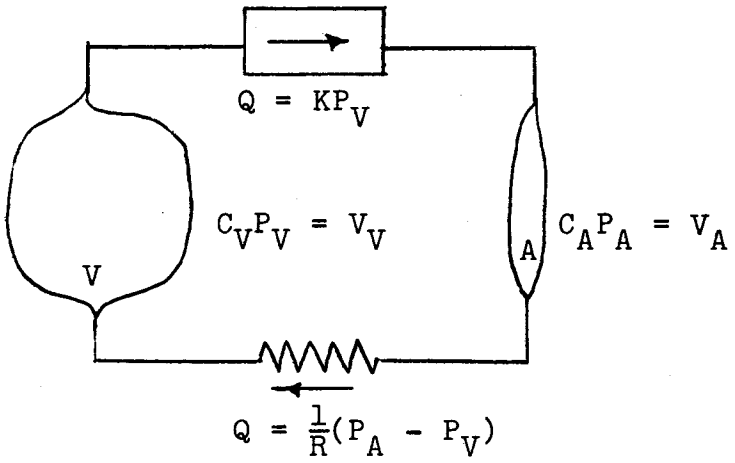
* Topham, W.S. & Warner, H.R., "The Control of Cardiac Output During Exercise" in Reeve and Guyton (Eds.) Physical Bases of Circulatory Transport: Regulation and Exchange, Saunders, Philadelphia 1967.

1967 v.47 B.S. Bevegård & J.T. Shepherd.

Models: The models to be presented here are for conceptual purposes only and represent simplified versions of a great variety of detailed models present in the literature. It is not clear whether the data justifies the kind of detail that is attempted in models of the whole circulation.

(1) The circulation without neural control at constant heart rate.*

In this model we regard the heart-lung as a system whose output is controlled by venous pressure.



$$V_o = V_A + V_V$$

* Guyton, Cardiac Output and Its Regulation

Q = Cardiac Output

P_A = Arterial Pressure

P_V = Venous Pressure

K = Ratio of Cardiac Output to Venous Pressure

R = Peripheral Resistence

C_A = Arterial Compliance

C_V = Venous Compliance

V_A = Arterial Blood Volume

V_V = Venous Blood Volume

$V_o = V_A + V_V$

The pair of equations which determine steady values of P_A, P_V are

$$C_A P_A + C_V P_V = V_o \quad \text{(Total volume constant)}$$

$$KP_V = \frac{1}{R}(P_A - P_V) \quad \text{(Heart flow = Tissue flow)}$$

The solution is

$$P_A = (1 + KR)P_V = \frac{(1+KR)V_o}{C_V + (1+KR)C_A}$$

$$P_V = \frac{V_o}{C_V + (1+KR)C_A}$$

Note that when $K = 0$ (Heart Stopped) $P_A = P_V = \frac{V_o}{C_A + C_V} = \bar{P}$.
This has been called the "mean systemic pressure" by Guyton.
The effect of heart action is to raise P_A above the mean systemic pressure and to reduce P_V below it.

The Cardiac Output is given by:

$$Q = KP_V = \frac{KV_o}{C_V + (1+KR)C_A}$$

Reduction of R leads to increased cardiac output up to the limit $Q = \frac{KV_o}{C_V+C_A}$. It is important to note that the mechanism of this increase is a shift of blood from the arteries to the veins with a consequent rise in venous pressure (stimulating the heart) and a consequent fall in arterial pressure.

This fall in arterial pressure is prevented by neural control, which we now consider.

The Controlled Circulation

In terms of the foregoing model, one could prevent the fall in arterial pressure by making K a function of R. In fact, the appropriate function is simply $KR = \alpha$, with α = constant >> 1. In terms of α, our expressions become

$$P_A = \frac{(1+\alpha)V_o}{C_V + (1+\alpha)C_A} \quad \text{(constant)}$$

$$P_V = \frac{V_o}{C_V + (1+\alpha)C_A} \quad \text{(constant)}$$

$$Q = \frac{V_o/R}{C_V + (1+\alpha)C_A}$$

Clearly in the foregoing control has been improved, since $Q \sim R^{-1}$, and the arterial and venous pressures are now constant. The question is: How does the circulation keep KR ≃ constant? The mechanism of the baroreceptor loop (see Page 223) would be

one means of doing this, but the following objections can be raised against this explanation:

(i) Attempts to open the baroreceptor loop and measure the open-loop gain have led to low values (e.g. 4) so one would suspect a substantial error to be present in the operation of the closed loop system, moreover

(ii) The "error" observed during exercise has the wrong sign. That is, blood pressure tends to rise which, by itself should tend to turn off sympathetic tone and reduce K; this is the opposite of what is required since R is low during exercise.

The answer to these objections appears to be* that there is central resetting of the "set point" for arterial pressure during exercise which roughly compensates (in fact slightly overcompensates, explaining the rise in arterial pressure) for the fall in pressure that would be expected with a low gain baroreceptor loop. This central resetting also seems to explain the anticipatory response to exercise which is sometimes observed.

Nevertheless it is tempting to speculate that the nervous system has some means of detecting peripheral resistance directly. It should be noted in this connection that the information sent to the brain along the nerves from the carotid sinus is far more extensive than a signal reflecting only mean blood pressure.

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* P.I. Korner, cited above.

Information concerning heart rate and the pressure pulse waveform is present in the baroreceptor's output, but the extent to which this information is used is not known. One interesting non-linear phenomenon appears when carotid sinus pressure is controlled independent of arterial pressure and the latter is measured: At constant mean carotid sinus pressure, pulsations in the carotid sinus reduce mean arterial pressure. This kind of response suggests the possibility that baroreceptor information is used by the nervous system in a complicated manner to compute and adjust the state of the circulation.

Without going into detail on the mechanism of control of arterial pressure, we can nevertheless construct a simple mathematical model for the controlled circulation by assuming that sympathetic tone is determined by the condition P = constant. Then if we go back to the model of local control by oxygen* we have the following equations

$$Q_i = \frac{P}{S} G_i + Q_i^*$$

$$Q = \frac{P}{S} G + Q^*$$

where

Q_i = flow to i^{th} tissue

$Q = \sum Q_i$ = cardiac output

Q_i^* = flow just sufficient to satisfy oxygen consumption of i^{th} tissue

$Q^* = \sum Q_i^*$

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* See pp. 220-222.

P = arterial pressure

S = sympathetic tone

G_i = constant characterizing i^{th} tissue

$G = \sum G_i$

Now the sympathetic tone S also regulates cardiac output; therefore we may write $Q = Q(S)$, and we can solve

$$Q(S) = \frac{P}{S} G + Q^*$$

for S and Q^* is given. Now suppose that the metabolic demand in one tissue (say i) changes by dQ_i^*. Since this is the only change, we have $dQ^* = dQ_i^*$ and

$$dQ_i = -\frac{PG_i}{S^2} dS + dQ_i^*$$

$$dQ = -\frac{PG}{S^2} dS + dQ_i^*$$

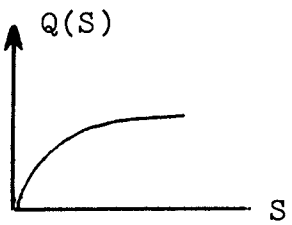
$$dQ_i - dQ = \frac{P(G-G_i)}{S^2} dS \quad .$$

The difference $dQ_i - dQ$ is the amount of flow which is redistributed to the i^{th} tissue from the others. Writing $dQ = Q'dS$ we have

$$dQ_i = \left[Q' + \frac{P(G-G_i)}{S^2} \right] dS$$

This expression shows that the increase in flow to the i^{th} tissue consists of two parts: an increase in cardiac output $Q'dS$ and a redistribution $\frac{P(G-G_i)}{S^2} dS$. Note that the ratio of increased output to redistribution is

$$\frac{Q'S^2}{P(G-G_i)}$$



For example, if $Q(S) = Q_o(1 - e^{-S})$ then $Q'S^2 \to 0$ for large S, so that in this case, with increasing severity of exercise, the body would shift from a mode of compensation involving increased output to a mode of compensation involving redistribution.

It is remarkable that the simple model proposed above exhibits centrally mediated redistribution without postulating that the central nervous system distinguish in anyway among the active and inactive tissues (all receive the same sympathetic tone S in this model)!

Long-Term Regulation of Arterial Pressure

This section will describe a theory of long-term control of blood pressure due to A.C. Guyton*. This theory has the remarkable consequence that steady state blood pressure is essentially independent of the activity of baroreceptors. Consequently, if this theory is accepted, changes in the properties of the baroreceptors cannot be the cause of hypertension, nor are such changes needed to permit hypertension in the face of some other stimulus.

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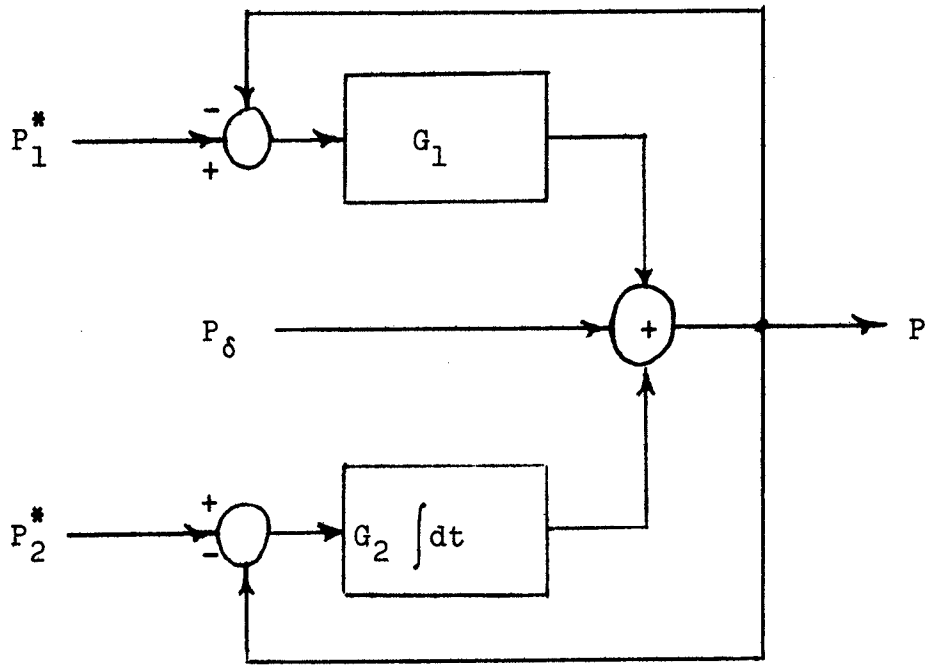
* Guyton, A.C., Cowley, A.W., Coleman, T.G., Clue, J.W.D., Norman, R.A., Manring, R.D.: Hypertension: A Disease of Abnormal Circulatory Control. Chest 65 328-338 (1974).

This theory is based on some interesting properties that arise when an instantaneous control system and an integral control system attempt to regulate the same variable.

Consider the control system shown:



An instantaneous control system (system 1) attempts to hold P at the reference level P^*, while an integral control (system 2) attempts to hold P at P_2^*. Meanwhile, P is also subject to a disturbance $P_\delta(t)$. The corresponding equation is

$$P = P_\delta + G_1(P_1^* - P) + G_2 \int^t dt'[P_2^* - P(t')]$$

If $G_2 = 0$ we have an instantaneous control system, with

$$P = \frac{1}{1+G_1} P_\delta + \frac{G_1}{1+G_1} P_1^* \quad .$$

For large G_1 this yields $P \approx P_1^*$, independent of P_δ. Changes in P_δ are reflected in P instantaneously, but reduced or "buffered" by the factor $(1 + G_1)^{-1}$. On the other hand, if $G_1 = 0$ we have an integral control system, satisfying

$$\frac{dP}{dt} = \frac{dP_\delta}{dt} + G_2(P_2^*-P)$$

Sudden changes in P_δ are reflected in P instantaneously and unbuffered, but if P_δ = constant, then $P \to P_2^*$ and the steady state error is zero.

With both systems working the differential equation for P is

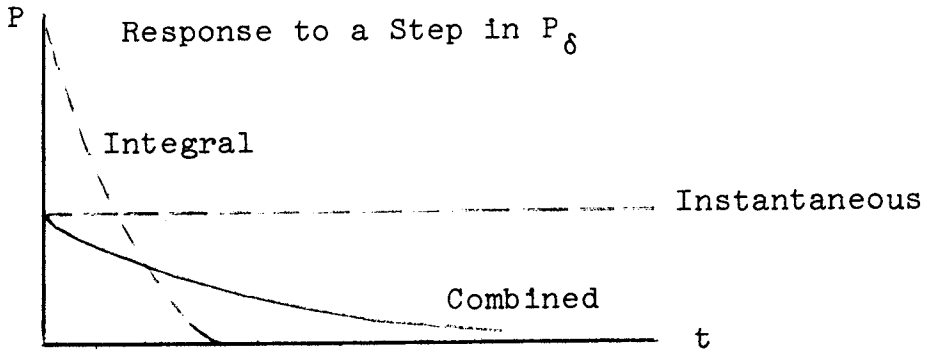
$$\frac{dP}{dt} = \frac{1}{1+G_1} \frac{dP_\delta}{dt} + \frac{G_2}{1+G_1} (P_2^*-P) \quad .$$

Note that P_1^* no longer appears. The properties of the composite control system may be summarized as follows

(i) Instantaneous disturbances (steps) are buffered by the factor $(1+G_1)^{-1}$.

(ii) If P_δ = constant, $P \to P_2^*$, independent of P_1^*.

(iii) The time constant for the approach of $P \to P_2^*$ is <u>increased</u> by the factor $(1+G_1)$. The approach to equilibrium is slower.



In applying these ideas to the circulation, Guyton regards the baroreceptor loop as the instantaneous system and the control of fluid volume by the kidneys as the integral control system. It is assumed, with some support from experimental evidence that the rate of urine formation depends on arterial pressure according to a renal function curve which has, in the physiologic range, the simple form $k(P_A - P^*)$. Then the rate of change of blood volume will be given by

$$\frac{dV_o}{dt} = D^* - k(P_A - P^*)$$

where V_o = blood volume, and
D^* = rate of drinking.

Remark on kidney physiology:

Urine formation begins in the glomerulus with separation of part of the plasma from blood. This is a pressure driven process, and the relevant pressure is the glomerular pressure P_G, minus the osmotic pressure of the plasma proteins which are left behind and the ions which are held back by the charges

on these plasma proteins. If this pressure is P_o, then we have a driving pressure $P_G - P_o$. It is therefore reasonable to expect a rate of glomerular filtration proportional to $P_G - P_o$. Now P_G is a fraction of the arterial pressure, the fraction being determined by the ratio of resistances in the afferent and efferent arterioles. Thus we may also write $P_G = \alpha P_A$ bearing in mind that α may not be constant. This allows us to expect glomerular filtration at a rate proportional to $\alpha P_A - P_o = \alpha[P_A - \frac{P_o}{\alpha}]$. It is important to note that most of the filtered plasma is ordinarily reabsorbed, although the fraction reabsorbed is extremely variable. If we assume, however, that the fraction reabsorbed does not depend on arterial pressure, then we have Guyton's result that urine formation is proportional to $k[P_A - P^*]$ where $P^* = \frac{P_o}{\alpha}$ and where both k and P^* may vary.

Next, we combine the model for control of blood volume outlined above with the simple model for short term control of the circulation outlined on page 229. The results are

SHORT TERM CONTROL

$$P_A = \frac{(1+KR)V_o}{C_V+(1+KR)C_A} \qquad \text{uncontrolled circulatory loop}$$

$$K = K(P_A) \quad K'(P_A) \leq 0 \qquad \text{baroreceptor control of heart}$$

$$\frac{dV_o}{dt} = D^* - k(P_A - P^*) \qquad \text{equation for blood volume.}$$

The equilibrium of this system is given by:

$$P_A = P^* + \frac{D^*}{k} \approx P^* \quad \text{for large } k.$$

independent of the properties of the function K(P) which describe the baroreceptor loop. Note that the steady volume <u>does</u> depend on the properties of K(P), however, since

$$V_o = P^* \frac{C_V+(1+KR)C_A}{(1+KR)} \quad \text{where } K = K(P^*)$$

Fluid retention in heart failure (low K) is predicted by this formula.

The equations given above can be linearized about their steady state to yield a linear control system like the one analyzed on pages 235-236. In particular, the baroreceptors will have the effect of buffering instantaneous changes but prolonging the eventual approach to equilibrium.

In terms of this model the parameters which most easily alter the blood pressure chronically are those which influence P^*. Among these we may list changes in the relative resistance of the afferent and efferent arterioles (such changes may be neural and even emotional in origin) and changes in the protein or ionic composition of the blood. On the other hand blood pressure (in this model) will be insensitive to changes in the heart, peripheral resistance (except in the kidneys), and baroreceptors. Whether or not blood pressure will be sensitive to fluid intake depends (in this model) on the slope of the renal function curve k. This correlates with the clinical

observation that blood pressure is not usually sensitive to fluid intake but becomes sensitive in patients with impaired renal function.