REVIEW ARTICLE
The obligatory role of the kidney in long-term arterial blood pressure control: extending Guyton’s model of the circulation

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Summary
We describe a model for the essential role of the kidney in long-term blood pressure regulation. We begin with a simple hydraulic model for the circulation, with a constant circulating volume. We show, with the help of a modification of Guyton’s classic diagram, that cardiac output and mean arterial pressure are functions of circulating volume, peripheral resistance, venous and arterial compliances, and the cardiac Starling curve. This approach models only acute changes in a ‘closed’ circulation – one where there is no intake or excretion of fluid. The model is then adapted to ‘open’ the circulation, include a role for the kidney, and represent more chronic changes. Arterial pressure is then a sole function of renal behaviour and daily sodium (and liquid) intake, and becomes independent of other cardiovascular variables. As well as generating specific hypotheses for further investigation, these models can be used for the purpose of education in cardiovascular control and the treatment of hypertension.

The problem: the kidney is ignored in many circulatory models

The circulation is commonly described using an analogy with Ohm’s law for an electrical circuit; the drop in pressure across the systemic circulation as blood flows from large arteries (pressure \( P_a \)) to central veins (pressure \( P_v \)) equals the cardiac output (\( \dot{Q} \)) multiplied by the peripheral resistance (\( R \)):

\[ P_a - P_v = \dot{Q} \times R. \]  

Educational reviews (e.g. ABC of Hypertension [1]) use this relationship to direct attention to elevations of \( \dot{Q} \), \( R \) or both to explain hypertension. A dominant UK textbook of medicine gives as the ‘mechanism of hypertension’ a ‘final common pathway…in the vessels that maintain peripheral resistance, as cardiac output is normal.'
in chronic hypertension’ [2]. This concept is widely repeated [3, 4]. Correspondingly, the drug treatment of hypertension is simplistically divided into drugs that affect \( Q \) and drugs that target \( R \) [4, 5]. The problem is that this modelling approach, whilst being mathematically consistent, is wholly misleading because it ignores the reality that, over the long term (days and months), blood pressure is regulated by renal mechanisms and \( Q \) becomes a function of blood pressure [6]. In short, in the long-term \( Q \) is a function of \( P_a \), which is set by the kidney. This reality has been long and patiently aired by a few experts in the field [7–9].

This paper attempts to introduce this essential role of the kidney in a way that we hope will become more popular. We explain how the cardiovascular system behaves in two different ways over different time scales. Equation 1 remains valid but we show how, in addition, the system behaves acutely as a ‘closed’ circulation and how it behaves chronically with different properties as an ‘open’ system. We will start our discussion with a simple hydraulic model.

**Representing the circulation in a simple model**

A simple ‘hydraulic’ model of the circulation illustrates how the variables in Eqn 1 are related (Fig. 1). The heart and lungs are represented by a circle (\( \bigcirc \)), through which blood flows from a reservoir representing the veins to a reservoir representing the arteries. The reservoirs are depicted as ‘beer glasses’; they are open to the air at the top, and the volumes of liquid in each container can be taken to represent the volume of blood in veins and arteries, respectively. The pressures of blood within the veins and arteries are respectively represented by the heights of the liquid levels in the reservoirs, \( P_v \) and \( P_a \). Thus the compliance of the veins \( C_v \) (the ratio of volume to pressure) is represented by the cross-sectional area of the venous reservoir, whilst the compliance of the arteries \( C_a \) is shown by the area of the arterial reservoir. Note that venous compliance is much greater than arterial compliance. \( P_v \) can in fact be visualised clinically as the jugular venous pressure, or measured directly as ‘central venous pressure’ (CVP). Stephen Hales first managed to visualise the arterial reservoir in 1732 by connecting a tall glass pipe to the carotid artery of a horse. He observed \( P_v \) directly as the blood rose to 8 feet 3 inches [10]. Today, we use an arterial catheter connected to a suitable transducer.

It should be noted that modelling the venous and arterial compliances with open reservoirs (see for example [11]) is entirely mathematically equivalent to modelling them with distensible tubes (see for example [12]), and each approach has its own appeal. In the case of the open reservoirs used here, the compliance of each reservoir is visualised by the cross-sectional area of the reservoir, as indicated above. If distensible tubes, enclosing liquid under pressure and having no free liquid surface, are used to model the venous and arterial compliances, then compliance (volume/pressure) is a property of the elastic wall of the distensible tube that cannot readily be visualised on a simple diagram like that of Fig. 1. Interestingly, the large veins, in which the degree to which they are filled with blood is directly visible in the jugular vein, are more physically similar to a reservoir with a defined surface, whilst the large arteries are more akin to distensible reservoirs with elastic walls.

Our simple model of Fig. 1 represents the circulation as ‘closed’ in the sense of containing a fixed volume of...
liquid. No mechanism exists in this model to permit entrance or egress of liquid. Consider what happens when the pump (\( \mathcal{O} \)) stops (Fig. 2), as it does at a cardiac arrest.

The pressures in the arteries and veins quickly equalise at what is called the mean circulatory filling pressure (\( P_{mcf} \)), which is found to be \( \sim 10 \) mmHg [13]. From this situation we proceed to deduce how the system functions when the heart is working normally.

Modelling the cardiac output: Guyton’s approach

Figure 1 showed us a heart connected to the vasculature. The problem of finding how the two components of the circulation together generate a certain cardiac output has been perplexing for the reason that (i) the output generated by the heart depends upon the pressures in the two reservoirs to which it is connected, and (ii) these pressures are in turn dependent upon the flow through the system, the cardiac output. The situation appears, literally, to be circular, as everything appears to be interrelated. Mathematically, solving simultaneous equations can find a solution, and Guyton suggested a most useful graphical approach to achieving this (Fig. 3).

![Figure 3 Depiction of the behaviour of the model circulation in Fig. 1 during a hypothetical experiment in which a pump replacing the heart is independently controlled as the flow through the pump (\( \mathcal{Q} \)) is increased from zero. In this experiment the independent variable (\( \mathcal{Q} \)) is plotted on the horizontal axis and the dependent variable (\( P_v \)) is plotted on the vertical axis, according to the usual convention. As \( \mathcal{Q} \) is increased the height of liquid in the venous reservoir (\( P_v \)) falls from the value it has during zero flow (\( P_{mcf} \), Fig. 2) towards zero. When \( P_v \) reaches zero, flow can no longer be increased; this condition corresponds with the emptying of the venous reservoir in the model and collapse of the large veins in vivo. The gradient of the relationship can be shown to equal \(-R/(1 + C_v/C_a)\), where \( C_a \) and \( C_v \) are respectively arterial and venous compliances, and \( R \) is the peripheral resistance.

Guyton’s model is a refinement of Fig. 1 and we will explain it step-by-step. We first consider how the vasculature behaves on its own when connected to a pump, the flow of which we can independently regulate from zero up to values that are higher than the normal cardiac output. Starting with the situation shown in Fig. 2 we have zero flow (i.e. cardiac output = 0) and thus a venous pressure equal to \( P_{mcf} \).

We now consider what happens to \( P_v \) as we increase the flow through the pump (e.g. we restart the heart after a cardiac arrest).

For any steady flow \( \mathcal{Q} \) that we set through our controlled pump, there will be a new level of liquid in the venous reservoir that will be lower than \( P_{mcf} \). Correspondingly, there will be a new higher level of liquid in the arterial reservoir, above \( P_{mcf} \). For the venous reservoir of compliance \( C_v \) experiencing a change in pressure from \( P_{mcf} \) to a new lower pressure \( P_v \), the change in the volume of liquid in that reservoir equals \((P_{mcf} - P_v) \times C_v\). At the same time, the arterial reservoir experiences an increase in liquid volume equal to \((P_a - P_{mcf}) \times C_a\).

Because the reduction in volume of blood in the venous reservoir must equal the increase in the volume of blood in the arterial reservoir, we can write:

\[
(P_{mcf} - P_v) \times C_v = (P_a - P_{mcf}) \times C_a.
\]  

\( P_v \) falls below \( P_{mcf} \) as \( P_a \) rises above \( P_{mcf} \). The relationship between \( P_v \) and \( \mathcal{Q} \) is represented in Fig. 3, where, traditionally, the variable on the vertical axis (in this case \( P_v \)) is the dependent variable and the variable on the horizontal axis (in this case \( \mathcal{Q} \)) is the independent variable as we conduct the imaginary experiment of increasing the pump flow from zero to ever higher values and seeing how \( P_v \) changes.

The line in Fig. 3 representing how \( P_v \) falls as \( \mathcal{Q} \) rises is called ‘the venous pressure line’. The relationship between the fall in \( P_v \) and the rise in \( P_a \) as \( \mathcal{Q} \) is increased from zero depends upon the relative compliances of the veins and the arteries (\( C_v/C_a \)) as we can see from Eqn 2. If the veins are very compliant relative to the arteries (and normally they are about 20 times more compliant), only a relatively small pressure drop occurs in the veins as a substantial volume of blood is transferred from the veins to the arteries; in this case the venous pressure line in Fig. 3 will be shallow. If the veins are relatively ‘stiff’ or non-compliant then the venous pressure line in Fig. 3 will have a steeper slope. The precise gradient of the venous pressure line is obtained by taking into account the simultaneous truth of Eqs 1 and 2. By solving them we obtain the gradient of the venous pressure line as \(-R/(1 + C_v/C_a)\), as shown in Fig. 3. Note that \( R \) is the ‘total’ peripheral resistance in the systemic circulation. We can use \( R \) without specifying how this resistance is
anatomically distributed, though we know that most of it is associated with the microcirculation, especially the arterioles.

At very high pump flows (cardiac outputs), the venous reservoir will empty and \( P_v \) will approach a value of zero. We can sensibly depict this state in Fig. 3 by showing that \( Q \) reaches a vertical line and can increase no further. The physical equivalent in the large veins would be that they collapse as the intraluminal pressure falls below that in the surrounding tissues. In other words, the vasculature on the venous side sets an absolute limit to the maximum flow that can be generated around the circulation, however vigorous the pump.

Next, we consider the properties of the heart itself. Starling showed that the unstimulated heart’s output is largely a function of its filling pressure [14]. We know also that cardiac output can depend to some extent on arterial pressure (‘aftersload’). Guyton suggested that we ignore the latter and assume that the cardiac output is a function of \( P_v \). In such a case we can represent the function of the heart on a plot of \( Q \) against \( P_v \), and this relationship is depicted as the ‘Starling curve’ in Fig. 4. The imaginary experiment being performed here is one in which the pressure in the venous reservoir is being independently controlled and plotted as \( P_v \) on the horizontal axis whilst the resulting output from the heart is being plotted as the dependent variable \( Q \) on the vertical axis.

Having plotted the Starling curve on Fig. 4 we can now add the venous pressure line from Fig. 3 to this plot in Fig. 4 so that we can consider the requirement that, for the circulation as a whole, both must be simultaneously true. When the venous pressure line is depicted in Fig. 4, we note that it has a gradient of \(-(1 + C_a/C_v)/R\) and that the part of the line representing the maximal achievable cardiac output is now a plateau intersecting the vertical axis. Our two lines in Fig. 4 (the venous pressure line and the Starling curve) are like two ‘simultaneous equations’ or ‘simultaneous relationships’ for which we are trying to find the value of two variables \( P_v \) and \( Q \) that satisfy both relationships. It is no longer helpful to think in terms of an independent and a dependent variable because each variable is dependent on the other. The only condition that satisfies both relationships is where the lines cross, shown as an open circle. This refreshingly simple approach allows us to see clearly what variables affect \( Q \) and \( P_v \), and in what way. It is striking, for example, that the individual compliances of veins and arteries do not determine the behaviour of the system; it is the ratio \( C_v/C_a \) that is relevant. This aspect of the Guyton model is often misunderstood. For example, Reddi and Carpenter [11] tried to characterise the system in terms of just \( C_v \) and \( R \), coining the term ‘venous excess’ – a concept repeated in a recent editorial in an anaesthetic journal [15]. However, since they ignored \( C_a \), their analysis was incomplete. Furthermore, a longstanding debate about distinguishing between a ‘venous resistance’ and an ‘arterial resistance’ is seen to be pointless because, as we have seen above, it is the single whole peripheral resistance \( R \) that characterises the behaviour [16]. The model remains the focus of lively discussion in the anaesthetic literature [17].

**What determines arterial blood pressure in the short term (minutes to days): extending Guyton’s analysis**

Figure 4 is commonly used to depict Guyton’s analysis of the circulation; unfortunately it does not incorporate systemic arterial pressure. Above we set aside \( P_a \) in our discussion but we can now re-introduce it and extend Guyton’s analysis by drawing a line to represent arterial pressure, as shown in Fig. 5. This line passes through the point representing \( P_{mcf} \) on the horizontal axis and has a positive slope of \((1 + C_a/C_v)/R\). This result is obtained from the same solution of Eqs 1 and 2 used earlier to find the precise gradient of the venous pressure line. Note that, since \( C_v/C_a \) is usually much smaller than 1 (normally around 1/20 or 0.05), this ‘arterial pressure
line’ has a gradient that is almost equal to 1/R, and the precise ratio of the arterial and venous compliances has very little influence on the gradient of the line. This contrasts strikingly with the venous pressure line, which has a gradient that depends markedly on the ratio \( C_v/C_a \). Since \( C_v/C_a \) is always very much less than 1, this gradient is very close to 1/R. \( \dot{Q}_1 \) is referred to in the text.

The effect of vasodilatation in the extended model

We can see that \( P_a \) in this closed system is heavily dependent upon R. The common experience of a large acute drop in R secondary to the administration of anaesthetic agents or vasodilators can be represented in the extension of Fig. 5 shown in Fig. 6 panel (a):

1. since the slope of the venous pressure line is proportional to 1/R, this line will become steeper as R is reduced;
2. if the Starling curve is unchanged, as will be the case if no reflexes have been activated, the point of intersection of this new venous pressure line with the Starling curve will lie higher on the graph, so \( \dot{Q} \) will increase from \( \dot{Q}_1 \) to \( \dot{Q}_2 \);
3. since the slope of the arterial pressure line is also proportional to 1/R, its slope will also increase. Thus the new, higher value of \( \dot{Q} \) will be associated with a reduction in \( P_a \) from \( P_{a1} \) to \( P_{a2} \).

In summary, the new scenario characterising an isolated fall in R will involve a higher \( \dot{Q} \) and \( P_v \), and a lower \( P_a \). Note that vasodilatation in the presence of a flatter Starling curve (e.g. an impaired or failing heart) will produce a greater drop in \( P_a \) for any degree of vasodilatation (Fig. 6 panel b). This seems consistent with extreme lability of blood pressure in some patients with poor cardiac function when exposed to the vasodilatory effects of anaesthetic agents.

The advantage of using Guyton’s adapted approach over simply using Eqn 1 is clear: while Eqn 1 suggests a fall in blood pressure with a vasodilator, Guyton properly predicts the additional rise in \( P_v \) and \( \dot{Q} \) and also incorporates cardiac function into these responses. Note that, in this particular example, it has been assumed that ‘vasodilatation’ refers exclusively in the model to a reduction in R without any change in \( C_v \) or \( C_a \). We shall see below that a reduction in R arising from a drug that dilates both arterioles and veins will be accompanied by ‘venodilatation’ and hence an increase in \( C_v \) resulting in a more complicated change in the circulation. Furthermore, during exercise, a reduction in R is accompanied...
by ‘venoconstriction’ and a decrease in \( C_v \), again leading to a different outcome from that induced by an isolated reduction in \( R \).

**The effect of blood volume, venodilatation and vеноconstriction in the extended model**

We can similarly use Fig. 5 to predict how \( P_a \) depends upon \( P_{mcf} \) and \( C_v/C_a \). The figure leads to a particularly interesting deduction if we examine the relationship between the volume of liquid in the vasculature of the model circulation (\( V \)), \( P_{mcf} \), and the total compliance of the vasculature (\( C_a + C_v \)). During a cardiac arrest (Fig. 2) the volume of liquid in the venous reservoir is \( C_v \times P_{mcf} \) and the volume of liquid in the arterial reservoir is \( C_a \times P_{mcf} \). If we add these together, we can say that the sum \( [P_{mcf} (C_a + C_v)] \) equals the total volume of liquid \( V \) in the vasculature at all times, because that volume is the same for all values of \( \dot{Q} \) in our closed system. Hence, we write:

\[
P_{mcf} = \frac{V}{(C_a + C_v)} = \left( \frac{V}{C_a} \right) / (1 + C_v/C_a). \tag{3}
\]

For simplicity we have ignored the volume of blood in our model that is not in either the venous or the arterial reservoir. If we assume that blood elsewhere has a constant volume, this will not affect the predicted behaviour of the model.

Considering the expression for \( P_{mcf} \) in Eqn 3, we can calculate the maximum possible cardiac output (i.e. the point where the venous pressure curve intersects the vertical axis in Fig. 5) to be \( V/(C_a \cdot R) \); we note with interest that this expression is independent of \( C_v \). It follows that the effect in the model of varying degrees of pure venodilatation (an increase in \( C_v \)) will be to generate a ‘fan’ of venous pressure lines passing through a fixed point on the vertical axis of Fig. 5 [where \( \dot{Q} = V/(C_a \cdot R) \)], the lines having ever steeper gradients as \( C_v \) is increased (Fig. 7). This may reflect the main action of venodilator drugs such as glyceryl trinitrate, which reduce \( P_v \), \( \dot{Q} \), and cardiac oxygen requirements and thereby relieve angina.

In what in vivo situation would venous constriction (a decrease in \( C_v \)) serve the needs of the body? Interestingly, Sheriff et al. were able to generate venous pressure lines in resting and exercising dogs using artificial cardiac pacing to control cardiac output [18]. They observed large parallel shifts in venous pressure lines going from rest to exercise equivalent to a large increase in \( P_{mcf} \) in Fig. 5, but with no change in the gradient of the venous pressure line [(\( 1 + C_v/C_a \))/\( R \)]. This can only be achieved with concurrent similar degrees of venous constriction (to decrease \( C_v \)) and arteriolar dilatation (to decrease \( R \)). This highlights the role of circulating adrenaline during exercise, which is known to be able to vеноconstrict via \( \alpha_1 \)-adrenoceptor agonism whilst generating arteriolar dilatation via agonist action at \( \beta_2 \) receptors in the large skeletal muscle bed.

In summary, by using Guyton’s model of a ‘closed circulation’ and then extending it a little (Figs 1 and 5), we have been able to interpret acute changes caused by drug therapy, exercise and autonomic blockade [18]. However, we do need to improve even upon this extended model.

**The open circulation: a novel model**

Since the circulation takes in and disposes of several litres of fluid each day, it cannot be regarded as a closed system over prolonged periods. The ‘open circulation’ is a system in which the volume of liquid can change. We represent the open circulation in the novel manner shown in Fig. 8. The daily intake of liquid is represented by a tap pouring liquid into the venous reservoir. The kidney is represented as a hole or series of holes in the arterial reservoir, from which liquid leaves the model circulation under the influence of gravity. No liquid leaves the circulation until the liquid level in the arterial reservoir \( (P_a) \) reaches the level of the lowermost hole. The distribution of holes can be engineered to represent the form of the pressure–natriuresis properties of the kidney (see below), but the precise way in which this can be done is beyond the scope of this review.
Over days and weeks, a defining requirement of our circulation is that loss of liquid (mainly via the kidneys) must equal intake (mainly from the gut). Otherwise, dehydration or severe fluid retention results. The kidney displays an elimination of salt and water that is dependent on arterial pressure \([19]\), sometimes over a very narrow range of pressure \([20]\). A most elegant demonstration of this was by Hall et al. in 1980, whose results are shown in Fig. 9 \([19, 21]\).

Three groups of six dogs were each studied over a period of 4 weeks. For each week, daily dietary sodium intake was controlled at a constant value and water was freely available. Sodium intake was increased weekly to provide four measurements spanning a very wide range of dietary sodium, from well below to well above normal. At the end of each week, urinary sodium excretion matched dietary intake closely, and the mean arterial pressure \((P_a)\) was plotted against excretion. Figure 9 shows the results for the three groups: controls, dogs with inhibition of angiotensin converting enzyme (ACE) inhibition with captopril, and dogs with constant infusion of angiotensin II.

In controls, \(P_a\) was largely independent of sodium intake and excretion, i.e. blood pressure was tightly regulated around a mean of \(\sim 100\) mmHg, while sodium was excreted in proportion to intake. Pharmacological disruption of normal renal mechanisms resulting in either low or high activity of angiotensin II revealed an underlying ‘pressure natriuresis’ phenomenon in which \(P_a\) depended quite markedly upon sodium intake and excretion. Thus, when angiotensin levels were low (with ACE inhibition), blood pressure was not simply lower for all levels of sodium intake and excretion; rather, blood pressure depended upon sodium excretion in a very specific way: \(P_a\) was lower than normal at low sodium excretion but similar to normal when sodium excretion was high. Conversely, when background angiotensin levels were high, \(P_a\) was similar to control when sodium excretion was low but much higher than control when sodium excretion was high; natriuresis was maintained, but at higher \(P_a\). The conclusion is that it is not the blood pressure that is being tightly regulated in these conditions; rather the body is obliged to match sodium excretion with sodium intake at the expense of changes in \(P_a\).

The model of Fig. 8 can be adjusted to represent these three conditions precisely, as indicated by the three arterial reservoirs depicted in Fig. 9. In the normal state,
Consequences of the model for the understanding of hypertension in vivo

Over short periods of time, when relatively little fluid enters or leaves the circulation, the system behaves just like the closed system. $P_a$ goes up and down as $R$, $C_v$, the Starling curve, etc. are varied and Fig. 5 models the relationships. Over longer time periods, however, the volume of liquid in the vasculature ($V$) does not remain constant and this open system behaves very differently. After any initial disturbance in liquid balance, equality of intake and output is gradually restored, a new steady state is attained, and arterial pressure can no longer be regarded as a function of $R$, $C_v$, the Starling curve etc.; it becomes a function of the properties of the kidney and the magnitude of the daily intake of liquid. Equation 1 is still valid, but what happens now is that $Q$ and $P_a$ adapt to accommodate a value of $P_a$ that is determined by intake and renal function. The volume of fluid in the system, $V$, becomes a variable that depends upon $P_a$.

A striking consequence of this behaviour is that, in the long term, an isolated change in $R$ produces no long-term change in $P_a$. This can be demonstrated with the aid of a modification of Figs 5 and 6 to show the progressive changes that occur in the circulation immediately after $R$ is reduced, and after a longer period of time during which equilibrium is restored between input to and output from the circulation; this is shown in Fig. 10.

The initial systemic arterial pressure is $P_{a1}$ and the initial cardiac output is $Q_{1}$, as represented by point 1 on the bold arterial pressure line. Upon a reduction in peripheral resistance (depicted as an approximate halving of $R$ by the arrows labelled A), the venous and arterial pressure lines increase their gradients (for reasons we discussed above), a new cardiac output $Q_2$ results, and arterial pressure falls acutely to $P_{a2}$, as depicted by point 2. This is the same sequence of acute changes that we saw in Fig. 6 panel (a). In the open system, this is now a non-equilibrium situation; the daily intake has not changed yet the daily urine output has fallen because of the lower arterial pressure (Figs 8 and 9). Gradually over hours and days the circulation fills (depicted by arrow B). The increase in volume in the circulation leads to a rise in $P_{aout}$ according to Eqn 3 (a cardiac arrest in a full circulation yields a

\[
V \rightarrow V + \Delta V, \quad P_a \rightarrow P_a + \Delta P_a
\]

Adding the change in volume ($\Delta V$) to the existing volume ($V$) gives the new volume ($V + \Delta V$), and the new arterial pressure ($P_a + \Delta P_a$) is the result of the sum of the old arterial pressure ($P_a$) and the change in arterial pressure ($\Delta P_a$). Therefore, the new arterial pressure ($P_a + \Delta P_a$) is equal to the old arterial pressure ($P_a$) plus the change in arterial pressure ($\Delta P_a$).
higher \( P_{\text{mcf}} \) than a cardiac arrest in an empty circulation), until \( P_{\text{mcf}} \) has increased from \( P_{\text{mcf1}} \) to \( P_{\text{mcf2}} \), at which value arterial pressure has been restored to \( P_s \), as represented by point 3. Note that in this final state, the gradients of the venous and arterial pressure lines have not changed from the state represented by point 2.

**Consequences of the model for the treatment of hypertension in vivo**

The ‘open model’ (Fig. 8) focuses our attention on the final common pathway that determines arterial pressure: i.e. the kidney, not the heart or the peripheral resistance. This model also demands that we ask searching questions about therapy. Antihypertensive drugs can only lower arterial pressure in the long term both in our model and in vivo so far as they alter the renal relationship between \( P_a \) and urine output, the pressure–natriuresis (PNS) curve (Fig. 9); we must therefore focus on the drugs’ renal vascular and tubular effects rather than their general effects on \( R \), \( V \), \( C \), etc. Three categories of agent have been proposed, according to how they affect this PNS curve (Fig. 11) [22].

The first group, probably including all vasodilators such as calcium antagonists, \( \alpha \)-blockers, endothelin antagonists and hydralazine, shifts the PNS curve downwards to lower pressures without changing the slope (Fig. 11, continuous grey line). The mechanism appears to be analogous to the surgical removal of a renal artery stenosis in secondary hypertension [23]; it is known, for example, that nifedipine preferentially dilates the afferent arteriole to the glomerulus compared with the efferent arteriole from the glomerulus [24]. In the case of \( \alpha \)-blockers, a pure vasodilatory effect may be modulated by a direct inhibition of tubular sodium resorption [25], supplementing the vascular antihypertensive effect with one similar to that of the diuretic group discussed below.

The second group, consisting of \( \beta \)-blockers and angiotensin–converting enzyme inhibitors, shifts the PNS curve downwards to lower pressures whilst also increasing its slope (Fig. 11 dashed line), the former group acting via the renal sympathetic nerve modulation of the renin–angiotensin system [23, 26]. This kind of action is illustrated by the data for ACE inhibition in Fig. 9. Because the blood pressure is sensitive to sodium intake, patients taking this kind of medication may benefit particularly from salt restriction in addition to drug therapy. We can predict that centrally acting agents such as \( \alpha \)-methyldopa will act in a similar manner by reducing renal sympathetic efferents, and this prediction could be tested experimentally.

Finally, a third group of agents, the diuretics, can decrease the slope of the pressure–natriuresis curve, with or without shifting its intercept to lower pressures (Fig. 11 dotted line) [27]. This kind of response is shown in Fig. 12 for a study in which eight otherwise untreated hypertensives were administered a thiazide diuretic. We note the striking steepness of the control line in Fig. 12, indicating that untreated hypertensives may show a marked dependence of arterial pressure on sodium intake, a feature that has been incorporated schematically into Fig. 11. Interestingly, \( \alpha_1 \)-adrenoceptor antagonists would be expected to combine the effect of vasodilators and diuretics because \( \alpha_1 \)-adrenoceptors mediate renal vasoconstriction as well as enhanced tubular sodium uptake. An appreciation of the distinct effects of different families of agents is likely to improve the rational choice of combination therapies.

![Figure 11](image-url) Effects of antihypertensive agents on the pressure–natriuresis curve for untreated hypertensives (—○—○—), according to the classification of Kimura et al. [22]. Pure vasodilators, such as calcium antagonists, tend to shift the pressure–natriuresis relationship towards lower mean arterial pressure (\( P_a \)) without a change of slope, by preferentially dilating the afferent renal arteriole; a similar effect is achieved by removal of a renal artery stenosis. Agents in the ACE-inhibitor group tend to shift the pressure–natriuresis curve to lower values of \( P_s \) whilst also increasing its gradient, as seen for captopril in Fig. 9. Drugs in this group would be expected also to include \( \beta_1 \)-adrenoceptor antagonists, centrally acting agents such as \( \alpha_2 \)-adrenoceptor agonists, and angiotensin II receptor antagonists because they all have renal actions predominantly via central or peripheral modulation of the renin–angiotensin system. The third group is that of diuretics, which shift the pressure–natriuresis line to lower values of \( P_a \) whilst decreasing its gradient, as seen for a thiazide in Fig. 12. Interestingly, \( \alpha_1 \)-adrenoceptor antagonists would be expected to combine the effect of vasodilators and diuretics because \( \alpha_1 \)-adrenoceptors mediate renal vasoconstriction as well as enhanced tubular sodium uptake.
lead to a fall in both cardiac work. Conversely, we can expect diuretics to mean arterial pressure (untreated hypertensive patients showed a marked dependence of function of sodium excretion. Data from [27]. Note that the 7 days of constant daily sodium intake of between 1 and 18 g NaCl and systemic mean arterial pressure plotted as a function of sodium excretion. Data from [27]. Note that the untreated hypertensive patients showed a marked dependence of mean arterial pressure (P) on sodium excretion, whilst thiazide administration reduced this dependence and also lowered P.

reduction in the circulating volume. The data of Fig. 12 suggest that it is more correct to think of the primary action of a diuretic as shifting the renal PNS curve to lower pressures; over time this then leads to a secondary reduction in circulating volume and hence P, and Q.

An important insight to be gained from these considerations is that different groups of antihypertensive agents can be expected to have different effects on the circulation (and other tissues) even if they achieve the same degree of long-term reduction in P. Thus, vasodilator antihypertensives that reduce R as well as shifting the PNS curve to lower pressures can be expected to induce a hyperdynamic circulation, with high P and Q, leading to an increase in cardiac work. Conversely, we can expect diuretics to lead to a fall in both P and Q as a consequence of their shifting of the PNS curve to lower pressures in the presence of a more constant R (though it is known that some diuretics have a vasodilator action as well). These changes can be estimated from appropriate use of Fig. 5. These different extrarenal actions may have their own therapeutic consequences.

In short, antihypertensives can only lower arterial pressure in the long term by ‘lowering the holes in the arterial reservoir’ of our model (Fig. 8), regardless of other widespread and interesting effects that they might have on the heart and vasculature. Knowledge of the way in which an antihypertensive agent modifies the renal PNS curve allows the clinician both to judge the way in which salt restriction can usefully form part of the patient’s management and to appreciate how agents from different classes might interact when administered together.

**Conclusion**

In the short term, in vivo blood pressure regulation can reasonably be predicted by the properties of a model of the closed circulation, for which Guyton provided a useful graphical solution in the 1950s. We have proposed a simple hydraulic model that visualises the key elements of this solution and extended Guyton’s graphical construction to represent arterial pressure (P) as a consequence of their specific hypotensive effects by reducing R, increasing C, and shifting the Starling curve of the heart. We believe that Guyton’s approach has not previously been clarified with regard to these variables in this way.

In the longer term, blood pressure is better regarded as a consequence of the balance between sodium (and liquid) intake and the prevailing renal pressure–natriuresis (PNS) relationship [28]. We have proposed an extension of our simple closed hydraulic model to visualise this phenomenon. It can be helpful to think in terms of V and cardiac output (Q) as being chronically a function of a value of P determined by the kidney (as well as by C, C, and R). Attempts to deny that the kidney is the ‘final common pathway’ for long-term regulation of arterial blood pressure are incorrect because they result in a violation of the simple requirement for mass balance within an open circulation [29].

As anaesthetists we are very familiar with seeing the immediate action of many classes of drugs on arterial blood pressure, but also appreciate the importance of long-term control of blood pressure to the perioperative and long-term wellbeing of our patients [30, 31]. It is almost an inconvenience that so many of the agents that have acute hypotensive effects by reducing R, increasing C, or shifting the Starling relationship for the heart (reducing contractility) are also agents that can have a chronic effect on arterial blood pressure via their specific renal actions. Generations of medical students have been encouraged to think in terms of a closed circulation by being told that ‘antihypertensive drugs act to reduce cardiac output and/or total peripheral resistance’ [32]. They may do, but that is not why they are
antihypertensives in the long run. The search for the causes of hypertension is helped by an understanding of the circulation as an open system. The search for an appropriate way to manage hypertension cannot progress without making a clear distinction between acute changes in the closed circulation and the more chronic changes in the open system [33]. In the teaching of medical students and trainees, we encourage the view of the renal PNS curve as central to the understanding of long-term blood pressure control. Our proposed open-circulation model (Fig. 8) can be used to visualise renal PNS function in a novel way.

References

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