GRAPHIC FORMAT FOR TEACHING LONG-TERM CONTROL OF SYSTEMIC ARTERIAL PRESSURE

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Circulatory homeostasis is a difficult notion. The graphic format presented here facilitates the teaching of long-term control of systemic arterial blood pressure and cardiac output. It is based on the view that the following four “function curves” cooperate in long-term regulation: the relation between blood volume and ventricular filling pressure, the relation between ventricular filling pressure and cardiac output, the relation between cardiac output and peripheral resistance, and the relation between arterial pressure and natriuresis. Positioning the function curves in the format presented here clarifies their cooperativity. The distinction between a nonsteady state and a steady state deserves emphasis. Long-term pathophysiology of the circulation is most easily taught on the basis of the assumption that, generally, there will be a steady state. The format clarifies why some known physiological relations are almost impossible to demonstrate in the intact organism, and it discourages explanations of pathophysiology that are not firmly based on physiology.


Key words: circulatory homeostasis; systemic arterial blood pressure; cardiac output; autoregulation of blood flow

Current theory holds that long-term control of arterial pressure consists of the interaction of the following three active organ functions: the Frank-Starling mechanism of the heart, pressure natriuresis of the kidney, and autoregulation of blood flow in the peripheral tissues (4, 5, 11, 12). Linked by the passive relation between venous volume and pressure, they define the homeostasis of the circulation.

Borst (4), who was the first to formulate the complete theory, gave credit to Starling (22) for his observation that excess fluid or fluid depletion is reflected in the volume of circulating blood and therefore in cardiac filling and cardiac output and to Starling’s view that renal fluid excretion is related to cardiac performance. Borst and Borst-de Geus (4) concluded that “Fluid balance and circulatory stability, therefore, are interdependent and maintained by one single regulating mechanism.” They also noted that, if the willingness of the kidney to excrete fluid is impaired, “a new equilibrium will be established at the expense of an excess of extracellular fluid and an excessive cardiac performance” but recognized that “Starling’s modified theory cannot explain why an increased cardiac performance results in a rise in arterial pressure, and not in an increased cardiac output.” Borst, therefore, theorized that the slight increase in arterial pressure associated with a clinically undetectable increase in cardiac output was enormously amplified by the increase in resistance that is due to autoregulation of blood flow by the peripheral tissues. “If all tissues react in the same way [i.e., autoregulate] . . . an increase in cardiac performance, not associated with an increase in demand [for flow by the peripheral
Innovations and Ideas

In the context of cardiovascular control, the rise in arterial pressure can ultimately be reflected in arterial pressure only, cardiac output will remain normal” (4).

Borst et al. (2–4, 7) formulated the theory of long-term cardiovascular control mostly on the basis of extended series of clinical observations. As is well known, however, experimental proof of the theory was largely the work of Guyton and his school (9, 10, 15, 17, 19), who validated almost every aspect of this integral control system.

Control systems of any kind are notoriously difficult to comprehend and, therefore, to teach. This is true of simple negative feedback proportional control devices, e.g., short-term baroceptor control of systemic arterial blood pressure (21) and even more so of integral control devices, such as the one under discussion, in which a deviation of arterial pressure from its steady-state value causes an opposite change in the rate of change of arterial pressure (12). I have found that comprehension (my own and that of others) is enhanced if one clearly separates the following two questions: first, if there is a deviation from the steady state, how does the control system return to its steady state? Second, how does one steady state differ from another steady state; for instance, how does a steady-state systemic arterial hypertension differ from a normal steady state? In fact, the greatest source of confusion is to neglect to specify whether one is considering a steady state or a nonsteady state. Both the nonsteady state and the steady state depend on the interactions of several organ functions. The graphic format presented here facilitates the explanation of those interactions.

Graphic Analysis

It is permissible and even desirable to gloss over the details of individual organ functions, since, by the time circulatory control comes up in the curriculum, we want to focus on the forest, not the trees. Figure 1, therefore, consists of four panels that illustrate greatly simplified versions of the physiological mechanisms that are involved.

Figure 1A shows the relation between blood volume and the filling pressure of the heart. (The conventional position of the axes in Fig. 1A is reversed for a reason that soon will become obvious.) Strictly, this relation should be a relation between blood volume and mean circulatory or mean systemic pressure (10), but the error introduced by omitting this refinement is tolerable. For filling pressure, one might use atrial pressure, ventricular end-diastolic pressure, or central venous pressure (some disease states excepted); the essence is that as blood volume increases, with everything else remaining the same, ventricular filling pressure also increases. Finally, we ignore for the time being that there are two filling pressures, one for the right and one for the left side of the heart.

Figure 1B shows a function curve for the left ventricle. It is best to plot cardiac output on the vertical scale, rather than stroke volume or stroke work. Although Fig. 1B basically depicts the Frank-Starling mechanism of the heart, in the long run, physiological degrees of ventricular remodeling in the form of “atrophy” or “hypertrophy” may play a role at least as great as that of the Frank-Starling mechanism, but that needs no emphasis at this stage.

Borst (4) referred to Sarnoff’s (20) work and recognized that “An increase in cardiac performance can be reflected in an increase in cardiac output, but also in a rise in arterial pressure.” We should, therefore, draw a family of Starling curves, each corresponding to a particular systemic arterial pressure but, again, this refinement can wait. Note that the abscissas of Fig. 1A and 1B, are the same.

Figure 1C shows the whole body autoregulation curve (9, 18). The reason for placing it to the right of the cardiac function curve is that the ordinates of Fig. 1B and C, are the same; in a steady state, cardiac output is equal to somatic blood flow.

Finally, Fig. 1D shows the relation between systemic arterial blood pressure and renal excretion (4, 14, 17, 22), a relation now called the “renal function curve.” Sodium excretion is shown as a function of systemic arterial blood pressure. Note that the abscissas of Fig. 1, C and D, are the same (systemic arterial pressure). It is not necessary to detail the individual physiological mechanisms that are responsible for the curve in Fig. 1D; in short, Fig. 1D represents the combined effects of the direct pressure natriuresis of the kidney, a...
sodium-conserving mechanism via the renin-angiotensin aldosterone loop, and a direct effect of angiotensin II on sodium retention by the kidney (5, 13–17).

The usefulness of arranging the function curves as arranged in Fig. 1 stems from the fact that the abscissas of Fig. 1, A and B, and of Fig. 1, C and D, are the same and that the ordinates of Fig. 1, B and C, are the same. The ordinates of Fig. 1, D and A, are not the same, but the ordinate of Fig. 1D is related to the first time derivative of the ordinate of Fig. 1A.

THE NONSTEADY STATE

The nonsteady state should be considered only one time, to demonstrate that the disturbed control system will automatically return to the steady state.

In class, I explain the automatic return to a new steady state in the following terms. It is incontestable that, in the long run, daily sodium intake (adjusted for nonrenal sodium losses) must equal daily renal sodium excretion. A normal level of adjusted sodium intake (equal to required sodium excretion) is indicated in Fig. ILL>. Assume that there is, at this time, a nonsteady state and that arterial pressure is below its steady-state value so that daily renal sodium excretion is less than the daily sodium intake, corrected for nonrenal losses. As the body excretes less sodium than is taken in, it conserves a negative ion also, for electrical neutrality, and body fluid osmolality rises. This sets off the antidiuretic hormone-mediated response, and the kidney will conserve water and so increase extracellular water volume. All other extracellular solutes, e.g., K⁺, Ca²⁺, Mg²⁺, glucose, lactate, amino acids, etc., have

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FIG. 1.
Arrangement of the 4 function curves. Scales are approximate. See text for explanation.
Level of required Na⁺ excretion indicated by horizontal broken line in D.
their own homeostatic controls and will increase in proportion to the increase in volume so that their concentrations in extracellular water remain the same, and the net result is an increase in extracellular fluid volume without much change in its composition. Part of the extracellular fluid volume is intravascular, diluting the blood, but homeostatic controls of plasma albumin concentration and hemoglobin concentration see to it that, as blood volume is increased, its protein composition, at least in the long run, remains unchanged. Thus the absence of equality of sodium intake and excretion in Fig. 1D ultimately causes a change in blood volume (Fig. 1A) and hence increases in cardiac filling pressure, in cardiac output (Fig. 1B), in tissue blood flow, in autoregulatory vascular tone (Fig. 1C), and in systemic arterial pressure (Fig. 1, C and D). As arterial blood pressure rises, renal excretion of sodium increases toward the level of intake. This process only ceases when, in a new steady state, blood pressure has risen far enough to cause the kidney to excrete sodium at exactly the rate at which it is taken in. The steady-state values of cardiac output, filling pressure, and blood volume can be found by connecting (Fig. 1, broken lines) the intersection of the required sodium excretion with the renal function curve. In Borst and Borst-de Geus’s (4) precise phrase, “The blood pressure will be maintained at the exact level required for the maintenance of sodium balance” (italics added).

Clearly, establishing a new steady state takes time, so much so that the competing mechanism, reflex control of pressure by the carotid baroreceptor mechanism (21), is given ample opportunity to adapt to a new reality (1).

Having demonstrated that the long-term control system generally returns to a steady state in which renal sodium excretion is equal to sodium intake, we can now use Fig. 1 to investigate the pathophysiology of the circulation. The point of departure of any analysis of long-term cardiac output and systemic arterial pressure always is the intersection point of the renal function curve with the corrected rate of intake of sodium ion because the system automatically returns to it when disturbed. Once this is understood and accepted, I advise my students to pay no attention to transient states when the disease they are considering is a chronic one. The steady state is easy to analyze, in both health and disease, and in almost all clinical situations that concern chronic disease, the patient will be close to a steady state. In the steady state, the intersection point of sodium intake with the renal function curve is the one certainty one always has; everything else follows.

STEADY STATES OF ABNORMAL CIRCULATIONS

Pathological states are characterized by changes in one or more of the function curves of Fig. 1. The first step of the analysis of a pathological state is to sketch the pathological function curve into the appropriate panel. The second step is to find the intersection point of the required rate of sodium excretion with the renal function curve. After that, other cardiovascular variables are determined by graphic analysis, as shown in the following examples.

Variations in sodium intake and salt sensitive hypertension. If sodium intake is suddenly elevated, there will no longer be a steady state. However, once enough time has elapsed for a new steady state to be established, blood pressure will have risen to a slightly higher level, and the intersection point of intake and the renal function curve (Fig. 2D) will have moved slightly to the right. Cardiac output (Fig. 2B) and blood volume (Fig. 2A) also will be slightly high. In practice, these effects will not be noticeable because the renal function curve is very steep (13, 14, 16) and the changes in the cardiovascular parameters with changes in sodium intake will be very small. Even in a steady state, it is difficult to demonstrate the relation between sodium intake and systemic arterial blood pressure. In spite of the fact that this relation is a very strong one. This apparent paradox bedevils the study of regulatory systems in intact organisms.

The situation is different in patients whose renal function curves are no longer steep. A common cause of this is random destruction of functioning renal tissue; when the remaining functional mass of renal tissue is only one-tenth of the normal mass, renal excretion of sodium, at any given arterial pressure, will be only one-tenth of normal (Fig. 3). In fact, Guyton and his co-workers (19) used resection of renal tissue exactly for the purpose of demonstrating by experiment that systemic arterial pressure does depend on the amount of salt that must be excreted...
per day (17), making the renal function curve less steep made the relation obvious.

Analysis begins by replacement of the normal renal function curve in Fig. 3D with the pathological renal function curve. The point of departure is the intersection point of the new renal function curve with the required sodium excretion rate. Following the lines in Fig. 3, one can see what the effects are on arterial blood pressure (elevated) and on cardiac output, filling pressure, and blood volume, which are essentially unchanged.

Figure 3 demonstrates that arterial blood pressure in patients with a reduced functional renal mass depends so strongly on the rate of salt intake that, unlike in the normal human, one can demonstrate clinically that, as salt intake is restricted, arterial pressure can be made to return to normal. It also demonstrates that, due to the flatness of the autoregulation curve (Fig. 3C), tissue perfusion and cardiac output, cardiac filling pressure, and blood volume are only minimally affected. Thus we can introduce two useful conclusions. First, the salt-sensitive nature of this form of hypertension is due to a renal function curve of reduced steepness. Second, and more generally, we see again that the more strongly one physiological variable controls another (e.g., Fig. 3C), the more difficult it is to detect the very existence of this dependency in the intact organism. When function curves are very steep, or very flat, one variable can change enormously with virtually no change in the other. As a consequence, blood pressure can change with little change in cardiac output or filling pressure. This apparent independence of one variable from another in vivo has led more than one student astray.
Salt-sensitive hypertension. Solid lines show steady-state result of a depressed renal function curve at a normal level of Na⁺ intake. Broken lines show possible therapeutic effect of a reduced Na⁺ intake.

Salt-insensitive hypertension. When the time has come to introduce the class to common forms of hypertension, my story goes somewhat as follows. A classic and simple example of a salt-insensitive hypertension is the bilateral Goldblatt (8) preparation (or the unilateral preparation with contralateral nephrectomy or a patient with a coarctation of the thoracic aorta). Figure 4 shows that the only difference with the normal situation is that the arterial blood pressure above the stenosis, e.g., the arterial pressure in the brachial artery, where it is conventionally measured, is no longer the pressure in the renal artery. The difference between the two pressures, that is, the horizontal distance between the two renal function curves in Fig. 4, is the pressure drop across the stenosis.

In every other way, the situation is unchanged. Again, the analysis of the steady state begins with the intersection point of salt intake with the pathological renal function curve, and from there it follows the solid lines in Fig. 4. For a steady state to exist, arterial blood pressure has to be elevated by exactly the pressure drop across the stenosis. Arterial pressure in these patients is not salt sensitive for the same reason arterial pressure in a normal individual is not salt sensitive; the steepness of the renal function curve allows an enormous adaptation in sodium excretion with changes in arterial blood pressure so small that they disappear in random biological and methodological variance.

As in the salt-sensitive hypertensive case, there must be an abnormally positioned (and/or abnormally
shaped) renal function curve for a long-term arterial hypertension to be present.

Essential hypertension may be a variation on this theme but awaits further study. It is incontrovertible, though, that patients with essential hypertension excrete a normal daily sodium load only when their arterial blood pressure is elevated and that, therefore, their renal function curves are displaced. The fact that such patients adapt to different salt loads with almost no change in arterial pressure is, again, due to the steepness of the renal function curve.

If long-term systemic arterial pressure is determined by the intersection of the renal function curve with the required rate of sodium excretion, it follows that, except in the salt-sensitive form of hypertension, long-term therapy of arterial hypertension can be effected only by therapeutic changes in the renal function curve. Such therapy can take the form of resecting an arterial stenosis or displacing the renal function curve, for instance, by paralyzing the renin-angiotensin system. Diuretics cause an upward displacement of the renal function curve (curve not shown).

Anemia and hyperthyroidism. We next have to make our students comfortable with the concept that, whereas systemic arterial pressure is essentially dictated by the kidneys, cardiac output is largely determined by the peripheral tissues. Again, the clinic offers instructive examples. If, as seems likely, tissue...
autoregulation of flow depends on the ratio of supply and demand, possibly of oxygen (9, 18), both a decrease in arterial blood oxygen content or an increase in tissue oxygen requirement would lead to an autoregulation curve that is displaced upward, i.e., at any given driving pressure, blood flow is increased compared with normal. As in all pathological cases reviewed so far, it is assumed that, to a first approximation, the other function curves remain unchanged.

Figure 5 shows the graphic analysis. Clearly, the main change is the increase in blood flow (cardiac output). Arterial blood pressure remains completely unchanged; changes in cardiac filling pressure and blood volume depend on the steepness of the cardiac function curve, which was assumed to remain unchanged. (Once the heart has adapted to the chronic flow overload, the upward change in its function curve will reduce the changes in filling pressure and blood volume.)

Figure 5 illustrates that, whereas systemic arterial pressure is determined by the renal function curve and its intersection with the required rate of sodium excretion, cardiac output is set by the autoregulation curve and its intersection with the blood pressure line derived from Fig. 5D. Depending on how “flat” the whole body autoregulation curve will be found to be (this is still not universally agreed upon), the steady-state systemic flow (equal to cardiac output) may not be very sensitive to arterial pressure. One may say, therefore, that blood pressure is set by the kidneys but that cardiac output (to a good approximation) is set by the tissues.
The failing heart. By now, the third class of clinical abnormalities, that of the inadequate heart, can be left as an exercise for the students as a test of the quality of our tutorial efforts. The failing heart is characterized by a lowered cardiac function curve. Once that fact is accepted, the graphic analysis (Fig. 6) should be self-explanatory.

A clinical nonsteady state. There is one important exception to the rule that patients with chronic disease generally will be in a steady state. Patients with severe heart failure (in fact, all cases of severe pump failure) may have cardiac function curves that are depressed to such a degree that their heart can no longer satisfy the flow requirements of the peripheral tissues at any filling pressure. Such patients cannot return to a steady state. Theory and the natural course of the disease agree that, without intervention, such patients continue to accumulate an ever-increasing excess extracellular fluid until edema or cardiac distension terminates life.

It should need no emphasis that acute cardiovascular malfunctions, such as are seen in the emergency room, result in nonsteady states and that the above steady-state analyses do not apply to them.

CONCLUSION

I believe that the above presentation has a degree of educational usefulness. Its strength is an emphasis on integration that permits it to fit together the essential interactions of the venous system, the heart, the peripheral tissues, and the kidneys. Those interactions constitute the circle of events that defines the physiology of cardiovascular homeostasis (4,12).
The clinical value of graphic analysis is that it discourages vague teleological associations between functional deficits, pathophysiology, and possible therapy.

As far as the origin of this analysis is concerned, I have not written anything that has not been written before, and I came upon this scheme by accident. In the early 1960s, I taught medical cardiovascular physiology in a lecture hall that had two side-by-side blackboards with another interchangeable set of two boards hung above them, all of them properly counterweighted for sliding up and down. Each board would hold one function curve. After all four curves had been sketched, Fig. 1 resulted without conscious effort on the part of the instructor. Naturally, a teaching aid so perfect and so inexpensive could not be allowed to endure, but it did inspire this analysis before being replaced by projectors and marker boards.

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