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Venous excess: a new approach to cardiovascular control and its teaching

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Reddi, B. A. J., and R. H. S. Carpenter. Venous excess: a new approach to cardiovascular control and its teaching. *J Appl Physiol* 98: 356–364, 2005. doi:10.1152/japplphysiol.00535.2004.—The circulatory control system is driven partly by factors relating to the arterial side and partly by factors relating to the venous side. Students are generally provided with a conceptually clear account of the arterial side, based on sound homeostatic mechanisms of negative feedback from a well-defined error signal, arterial pressure. However, on the venous side, teaching is often based on the notion of venous return, a concept that, as normally presented, is imprecise and intangible, a frequent cause of confusion that may lead to errors of clinical practice. Although one can trace these misconceptions back to some of Guyton's publications, Guyton himself was well aware of the complexities of venous resistance and capacitance but has not always been well served by subsequent misinterpretation. The fundamental problem with venous return that makes it inappropriate for controlling the circulation is that it lacks the essential requirement of being an error signal. We propose instead a new variable, venous excess, which represents the accumulation of any mismatch between the rate of blood entering the great veins and the rate of leaving, the cardiac output. As well as being directly observable without intervention (in a patient's jugular vein), it meets all of the requirements of an error signal: via the Starling mechanism it stimulates cardiac output, regulates venous compliance, and in the longer term is an important determinant of fluid intake and excretion, and these effects act to reduce the original perturbation. Based on this concept, we suggest a simple and secure basis for teaching the control of the circulation that avoids undue reliance on entities that are difficult to specify or measure and emphasizes the role of feedback and the similarities between the arterial and venous mechanisms.

feedback; homeostasis

WHY DOES THE CARDIOVASCULAR system seem to pose such conceptual problems to the medical student? Perhaps it is because of the multiplicity of homeostatic feedback mechanisms, some operating primarily on the heart and some on the peripheral vasculature, and some short term and some long term. It does not help that modern students have so little intuitive feel for flow, resistance, and capacitance, and an increasingly shaky grasp of the underlying physical principles (29). Ultimately it is the result of the circulation's intrinsic circularity, which is liable to confound cause and effect unless the subject is treated with logical rigor. Rothe (20) has even questioned whether the terms dependent and independent variable have practical meaning in the closed loop of the cardiovascular system. This is not mere academic hairsplitting, for a lack of causal clarity can have serious implications. Brengelmann (personal communication) reports instances of interns blindly applying what they dimly remember from their physiology classes, attempting to stimulate a failing heart by reducing right atrial pressure, on the grounds that this would increase venous return. All of this may reflect the fact that among

physiologists there is still debate and controversy about how some of these things should be viewed; but if it is true that patients are consequently at risk, then perhaps we should make more effort to agree on a conceptual framework. While, as for any physiological system, no such scheme can ever be complete in every detail (and would be less useful if it were), it does seem worth attempting to formulate a more secure conceptual basis on which a student might build to gain a better understanding of what is going on.

THE ARTERIAL ERROR SIGNAL

In constructing such a framework, a starting point that is frequently adopted is to recognize the distinctiveness of the arterial and venous sides of the circulation. One is distributive and the other collective, and this difference in function is reflected in their well-known physical properties and also in the relative independence of their control mechanisms (13, 19). On the whole, it is the arterial control system that is simpler, and better understood by students, in that it more obviously embodies a classic homeostatic regulatory mechanism involving negative feedback, the baroreceptor reflexes. Arterial blood pressure is an error signal because it represents a mismatch between the supply of blood by the cardiac output and the demand for blood by tissues. A local increase in demand, through vasodilatation, causes peripheral resistance to fall; at the same time, the increasing deficit means that arterial volume drops. For both of these reasons, arterial pressure will fall, and the baroreceptors will respond partly by increasing heart rate, so that cardiac output is raised, but also by regional vasoconstriction, diverting blood to more demanding areas from those that are less critical. There are many details of this system that are complex and not wholly understood, but, nevertheless, the clarity of the underlying negative feedback control system means that it is very hard for a student to misunderstand completely how arterial pressure is controlled and why it has to be controlled: a drop in blood pressure indicates that supply is not keeping up with demand.

But when we turn to the venous side of the circulation, things are very different. As normally presented, there is no error signal; instead, the student is introduced to the idea of venous return.

THE VENOUS SIDE: WHAT IS VENOUS RETURN?

The history of science is strewn with the debris of concepts that were once received opinion, in tune with the "common sense" of their time: such were phlogiston, the ether, vital spirits, and phrenology. With hindsight, we can see how they hindered understanding rather than advancing it and may be surprised that they could ever have become common currency; yet how difficult it is to perceive our own unthinking prejudices, the notions that are so familiar that we do not think of questioning them. Is it possible that "venous return" is such a concept?

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The output of the heart is largely determined by factors that depend on the venous side of the circulation. No one could reasonably quarrel with such a statement, established originally by Starling's classic experiments (15, 17, 30) and later confirmed in numerous laboratories all over the world. If one wishes to say, more snappily, that venous return governs cardiac output, then again there is little to quarrel with. Provided, that is, we realize that venous return implies no more than that, when other factors are held constant, an increase in the amount of blood being offered to the heart will stimulate an increase in its output. The desirability of such a self-regulatory system seems so obvious that it is a concept that students embrace immediately: venous return has a reassuring, engineery sort of sound to it that leads to a comforting sense of pragmatic tangibility. But is this confidence justified?

Yes, provided one does not try to be too specific about what exactly venous return actually is. Ask a few awkward questions, however, and things seem a little less secure. What units, for example, are we to measure venous return in? Most students have an intuitive feeling that it must be some sort of quantity of blood, somehow piling up around the heart. So is it to be measured in liters? Or does it represent a flow per unit time, in liters per minute, like cardiac output? That immediately sounds more scientific. But we can then ask another awkward question: where is this flow to be measured? Is it literally the flow of blood into the heart?

That sounds plausible and is probably what most clinicians would say but leads to a problem: if the blood flowing into the heart per minute is the venous return, in what way (unless the heart is punctured) can this be different from the blood flowing out of the heart per minute, in other words the cardiac output? The heart does not store blood to any significant extent: over periods of the order of a minute, what goes in must come out. In the words of the late distinguished cardiac physiologist Arthur Guyton (9), "Obviously, except under momentary conditions the venous return and the cardiac output must be equal." So defining venous return as the rate of entry of blood to the heart, though perfectly logical, is too circular to be of practical use. Is venous return then the flow of blood into the great veins, or possibly further back still, from the venules or even from the systemic capillaries? But the same argument, that what goes in must go out, applies with almost equal force at every point in the circulation. Provided there is no hemorrhage or net movement to or from extracellular fluid, or a persisting rate of change of vascular cross section, wherever we draw a line across the circulatory bed, the total flow across that line in a minute must necessarily be equal to the cardiac output. As Rothe (20) points out, to consider an increase in cardiac filling (a volume) as synonymous with an increase in venous return (a flow) leads to logical inconsistencies and unnecessary controversy.

Venous return, considered as a flow, is essentially a consequence and not a cause: it cannot in itself be controlling the heart. How did it ever come to be seen as such?

THE CLASSICAL EXPERIMENTS: STARLING AND GUYTON

The answer lies not in Starling's original experiments, which he described with complete physical accuracy, but with the well-intentioned, but often misleading glosses of later interpreters and textbook writers. Starling's primary contribution was, of course, the series of experiments on the isolated heart, devoid of its nerve supply (15, 17, 30). By raising or lowering an artificial venous reservoir, he was able to show that increased right atrial pressure resulted in increased stroke volume. This could be explained by postulating that the fibers of ventricular muscle contracted with greater force when stretched, the notion later to be known as Starling's law. Because the ventricles increase their force of contraction with increasing volume, they embody an intrinsic integral feedback control mechanism, in that accumulating ventricular excess stimulates a larger stroke volume until equilibrium is reached (or congestive heart failure intervenes). Thus Starling's law is about the ventricles rather than the atria: the atria simply deliver faithfully to the ventricles whatever has turned up in them, and what the law guarantees is that this volume will in turn be delivered as stroke volume. It is, in other words, an executive rather than control mechanism, significant in a sense only to the heart itself. The Starling mechanism cannot of itself determine stroke volume, which is governed by how much blood enters the right atrium and is delivered in each cycle into the ventricle; rather, it prevents accumulation by guaranteeing that this volume is expelled.

In the laboratory, we can manipulate this volume in different ways. We may alter the driving pressure, which, if the return resistance is small, will then determine right atrial pressure and thus atrial stretch, or we can increase the resistance to the point where it limits the rate at which blood is permitted to enter the right atrium: atrial filling will then also depend on the heart rate. Both of these methods were used by Starling as a way of altering atrial input: either, as described earlier, raising and lowering the reservoir to create different driving pressures, or altering return resistance with a constant "venous" head of pressure.

Now because raising the venous reservoir increased cardiac output, the rate at which blood would be drawn from the reservoir would increase as well. An unsophisticated observer might well form the impression that in some way it was this increased flow of blood into the heart that was causing the increased cardiac output (whereas, in fact, it was of course the increased right atrial filling, and consequent ventricular stretch, that was generating increased cardiac output and, inseparably, the flow of blood into the heart). One can well see how a muddled idea that increased venous return could stimulate cardiac output might arise, when in truth the critical variable is the degree of atrial distension. The futility of trying to propose a causative relationship between venous return and cardiac output was fully appreciated by Guyton (8), who concluded that "we would be arguing in circles to say which is more important, venous return or cardiac output." They are both interdependent and, except transiently, essentially equal: experimental manipulation of the heart that alters cardiac output will eventually influence venous return, whereas manipulation of the peripheral circulation that alters venous return will eventually influence cardiac output. However, in the accounts of Starling's experiments as portrayed in successive popular textbooks, one can see the misconception that venous return determines cardiac output taking root and being used to indoctrinate successive generations of medical students. Consequently, an elegant mechanism, relating two simple, measurable parameters (right atrial pressure and cardiac output), became obscured by introducing a redundant variable, venous

return, with little or no practical meaning: when medical students take to the ward, it is right atrial pressure (either directly measured through a central line as central venous pressure or visualized in the jugular vein) and cardiac output (again either directly measured or clinically estimated from signs of tissue perfusion) that they encounter, with not a "venous-returnometer" in sight.

It was the subsequent misinterpretation of another set of classic experiments (9–11) that finally enthroned venous return in medical teaching. The conventional account often to be found in textbooks, usually attributed to Guyton, is at first sight plausible enough and is along the following lines. We start with the arterial side of the circulation and apply the fundamental equation relating flow to resistance and pressure, equivalent to Ohm's law in electricity:

$$\text{Pressure drop} = \text{flow} \times \text{resistance (cf. } V = I \cdot R) \quad (1)$$

where V is voltage, I is current, and R is resistance. In the case of the arterial system, and taking the pressure at the far end of the resistive elements to be negligible in comparison with the mean arterial pressure, we have:

$$AP = CO \cdot PR \quad (2)$$

where AP is mean arterial pressure, CO is cardiac output, and PR is total peripheral resistance. Because, like electrical resistance, the latter is not something that can be independently measured, this equation is, in a sense, true by definition.

It is then natural to wonder whether there might exist some equivalent formula for the flow of blood on the venous side. Leaving aside the difficulties mentioned earlier with interpreting venous return as a flow, nevertheless, by analogy, we might pair cardiac output with venous return and peripheral resistance with some measure of overall venous resistance. Again this is not something that can be measured at all easily, but, as with peripheral resistance, we might hope to be able to derive it from the other variables. But there is a complication: whereas on the arterial side we could neglect the pressure at the far end, on the venous side this is not possible because the final pressure (right atrial pressure) is not very different from the average pressure in venules that in this scheme of things is imagined as driving the blood back to the heart. Proposed by Bayliss and Starling (1) as a variable reflecting the interplay of vascular volume and tone, this "mean systemic filling pressure" is taken, in the Guytonian formulation, to be a head of pressure at an unspecified location somewhere in the peripheral circulation. Although it has proved a useful experimental tool in the analysis of vascular capacitance by distinguishing "stressed" and "unstressed" volumes (7, 27), and identification of the pivotal pressure point allows analysis of the redistribution of blood within the vascular compartment (20), for clinical teaching its intangibility presents something of a problem and has become a further source of confusion to medical students. It can only be estimated in an experimental animal by using extreme measures, for example, inducing fibrillation (11), and cannot be measured at all in an intact patient. Furthermore, in a functioning circulatory system, its physical location will move around with changes in the distribution of vascular tone. Nevertheless, if we are prepared to disregard these rather fundamental problems, by analogy with the arterial equation we can write down the venous equation that is found in many textbooks:

$$(MSFP - RAP) = VR \cdot V\Omega, \quad (3)$$

whence:

$$RAP = MSFP - VR \cdot V\Omega \quad (4)$$

or:

$$VR = (MSFP - RAP)/V\Omega \quad (5)$$

where MSFP is mean systemic filling pressure, RAP is right atrial pressure, VR is venous return, and $V\Omega$ is venous resistance. This ability to rearrange equations at will is, of course, highly convenient, but it contains pitfalls, above all for the unwary medical student. On the arterial side, for instance, writing $AP = CO \cdot PR$ correctly represents the underlying causal relationship: arterial pressure is the dependant variable and is consequent on cardiac output and peripheral resistance. Clearly, this is mathematically equivalent to writing $CO = AP/PR$, but such a rearrangement makes functional nonsense: cardiac output is by definition the product of stroke volume and heart rate and is the cause of the arterial pressure, not its consequence. Yet how regrettably often medical students evoke this version to explain that hemorrhage causes a fall in cardiac output because there is a drop in arterial pressure. When we turn to our set of three venous equations, the same considerations apply: only one of them can represent the true, functional state of affairs. Which?

The answer to that question lies in the experiments from which Guyton obtained his famous venous return curves that emphasize the relationship embodied in *Eq. 5*, which implies that venous return is a consequence of right atrial pressure, rather than its cause. Two classic papers (10, 11) describe the experiments from which the venous return curves for the dog were obtained. In one experiment, in a recently dead animal, the heart was bypassed by a pump and flowmeter; in another, the flow from the vena cava was intercepted by the same pump/meter combination and sent to the right atrium. In both cases, the right atrial pressure was estimated by passing the blood through a thin-walled section of tubing, which could be raised or lowered to determine the height at which collapse just occurred (these arrangements are particularly clearly described and illustrated in Ref. 2): an ingenious device, but its use had the unfortunate consequence that to a superficial reader it can well seem as if Guyton was raising and lowering this indicator to generate different right atrial pressures, which was not the case. What only becomes apparent by relatively careful reading of the papers is that the independent variable was always flow (as set by the pump, which of course also determined cardiac output), and right atrial pressure was what was measured. Guyton drew his graphs with right atrial pressure as the abscissa and venous return as the ordinate; unfortunately, this led many commentators to nurture the belief that he had demonstrated that right atrial pressure "determined" venous return, when in fact it was the other way around. A particular right atrial pressure was chosen as a target, the collapsible tubing raised to the required height, and then by trial and error a pump speed was found at which this desired pressure was achieved. In other words, Guyton altered flow into the right atrium to achieve a given right atrial pressure. As he increased the flow, right atrial pressure decreased. The curves were presented as if it were right atrial pressure governing venous

return rather than the other way around, encouraging the common misconception that lowering the right atrial pressure in effect sucked more blood through the supposed resistance of the veins. We now realize the true mechanism: that increasing the flow results in arterial accumulation and, therefore, venous deficit (16). The right atrial pressure falls because of the reduced volume, emphasizing the fact that, on the venous side, it is not so much resistance and flow that matters, as capacitance and volume. These parameters, so often ignored in cardiovascular teaching, are, we shall argue, fundamental to the control of the heart.

Nevertheless, Guyton's achievement was to demonstrate a relationship between right atrial pressure and venous return, and even if it was, in functional terms, originally presented the wrong way around, one can still combine it graphically with the (real and measurable) Starling relationship between right atrial pressure and cardiac output to create the well-known diagrams purporting to explain the regulation of cardiac output that every medical student is made to reproduce (Fig. 1A). Can something so universally accepted and taught be wrong?

Clearly there are some aspects of this diagram that do not depend on what causes what and are helpful in understanding the regulation of the circulation. The steady-state equilibrium can only be where the two curves cross, and, if we know how the curves are influenced by neural or endocrine factors, or by disease, then we can predict how this equilibrium point must move. But this necessary mathematical feature tells us nothing about how the heart is actually regulated by disturbances on the venous side. We argue that the conventional interpretation is in fact misleading in a number of respects. Some have already been mentioned: first, that two of the variables cannot be measured; and second, that, because venous return must in the longer term necessarily be equal to cardiac output, a causative relationship cannot be derived. It is not surprising if students leave the classroom believing that increasing venous return increases cardiac output and that increasing right atrial pressure decreases venous return (Guyton) yet increases cardiac output (Starling), whereas venous return and cardiac output must be identical anyway!

THE IMPORTANCE OF CAPACITANCE

But, in addition, this model has fundamental flaws that have to do with the underlying physics. *Equations 3–5*, purporting to describe the flow of venous blood, by analogy with the arterial side, are based entirely on consideration of flows and resistances: they take no account of either volumes or capacitances. An electrical analogy can be helpful in appreciating the underlying physical relationships between these variables (see, for example, Ref. 2). Passive electrical circuits consist of capacitors as well as resistors. A large capacitor can absorb a lot of charge with little change in potential; a compliant vessel (with
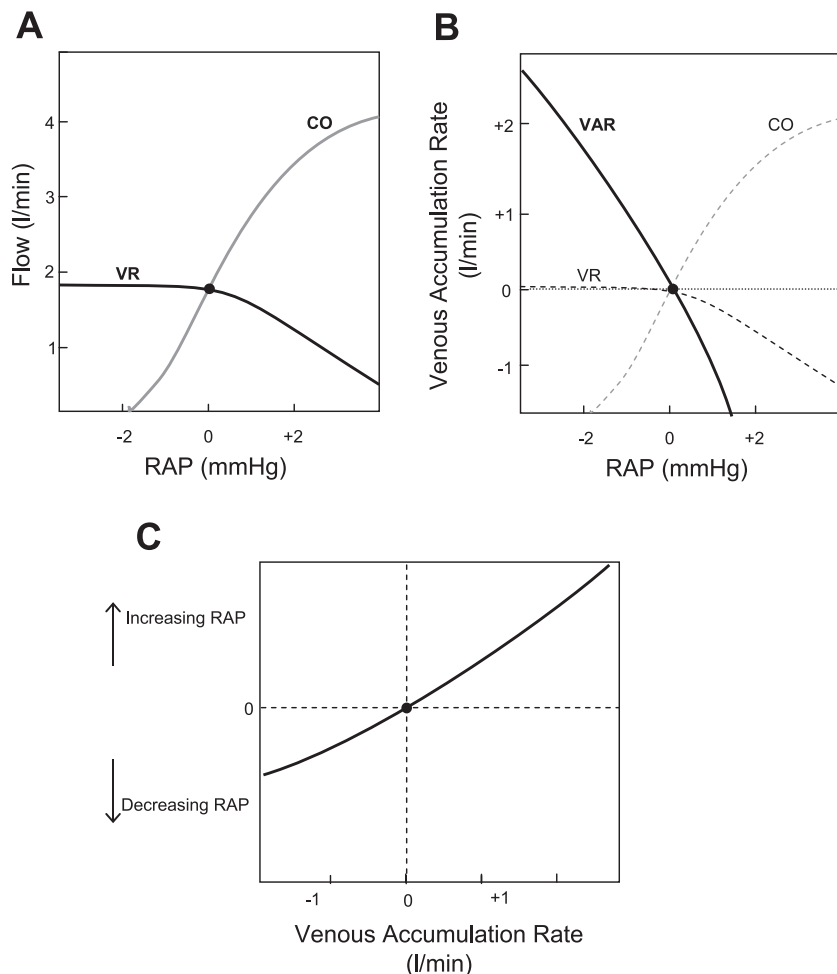

Fig. 1. *A*: classic schematic representation of the relationship between right atrial pressure (RAP) and cardiac output (CO)/venous return (VR) [after Guyton (9): canine]. The dot represents the equilibrium when CO = VR, which must necessarily be true in the long term. In the short term, however, they may differ, with the rate at which inflow exceeds outflow being the venous accumulation rate (VAR) (*B*). In general, the time integral of VAR is venous excess (VE), a fundamental circulatory variable; thus positive VAR will lead to growing venous distension and increased RAP (*C*).

high capacitance) can store much blood with little increase in pressure. In the case of flow (of current or fluid) we have:

$$\text{Voltage drop} = \text{current} \times \text{resistance} \ (V = I \cdot R) \qquad (6)$$

$$\text{Pressure drop} = \text{flow} \times \text{resistance} \ (P = F \cdot R) \qquad (7)$$

Whereas for quantities (charge or volume) the relationships are:

$$\text{Voltage} = \text{charge/electrical capacitance} \ (V = Q/C) \qquad (8)$$

$$\text{Pressure} = \text{volume/fluid capacitance} \ (P = V/C) \qquad (9)$$

Real blood vessels, like real electrical conductors, necessarily have both resistance and capacitance; these properties are distributed along their length, varying both from place to place and over time. To be practically useful, equations describing the system as a whole must necessarily make simplifications, either by lumping together parameters that are in truth spatially distributed, or by acknowledging that some factors are negligible in comparison to others. The problem in basing a venous formula for blood flow on the arterial one is that the latter makes an assumption that is acceptable for the arterial side of the circulation but not for the veins: it ignores capacitance. On the arterial side, this is only of secondary consequence. The small arterial capacitance means that its effects can, with two notable exceptions, be neglected, and the pure Ohmic formulation will do perfectly well. One exception is, of course, as Hales pointed out as long ago as 1733, that it irons out the pulse (12). The second exception is an important one, because it has given rise to an observation that has been used to lend weight to the Guytonian formulation. If the sympathetic supply to the heart is stimulated, cardiac output increases. This leads to arterial distension and an increase in arterial pressure. As a consequence, the quantity of blood in the central veins is reduced, and right atrial pressure falls. This fall is due to capacitance, not to resistance: a shift in a volume of blood, not a flow. It is this effect that is actually the cause of the falling part of Guyton's venous return curve (2, 23). Furthermore, although the compliance of arterial vessels varies considerably, the relatively small proportion of the blood volume in the arterial system compared with the venous system means that changes in arterial compliance are not believed to contribute significantly to the central control of the circulation (33).

But turning to the venous side, things are very different. The venous system is distributed in an extremely complex way, and its properties vary substantially from one site to another (21, 23). Nevertheless, it is clear that, far from being negligible, the capacitance now dominates the entire venous behavior: as both Levy (16) and Tyberg (32) point out, the central venous pressure (and thus right atrial pressure) is, to a great degree, essentially determined by venous capacitance. Indeed, apart from some exceptional conditions such as positive pressure ventilation, it is now the resistance that is the less significant. We can see this must be so by considering the effect of sympathetic venoconstriction, one of the most profound regulators of cardiac output; even the stress of mental arithmetic is enough to cause a significant decrease in venous capacitance (18). Not all parts of the venous system are equally under sympathetic control, but, if we consider the lumped capacitance of the entire system, it is clear that venoconstriction, particularly by reducing the venous unstressed volume [that is,

when the distending pressure is zero (21)] but also by reducing venous compliance generally, must raise venous pressure and thus right atrial filling and cardiac output. Yet *Eq. 5* predicts the opposite: as Guyton explicitly states in the 1955 paper in the *Physiological Review* (9), ". . . the greater these dimension [i.e., of the peripheral circulatory system], the greater will be the venous return." Thus increased venoconstriction, for instance in exercise or stress, should increase venous resistance and thus reduce right atrial pressure and cardiac output. This is not, of course, what actually happens, either experimentally or in clinical practice. Clinicians treating cardiac failure routinely use venodilating drugs to relieve the right atrial pressure overloading the heart. Decrease in venous capacity has been shown to be the primary stimulant to cardiac output when the carotid baroreflex is elicited, whereas venous resistance is not significantly affected (6, 13).

AN ERROR SIGNAL: VENOUS EXCESS

If we agree that it is venous resistance rather than venous capacitance that can more safely be neglected, then it follows that it is not venous return (as a flow), but volume that predominantly controls right atrial pressure and thus cardiac output. From a control systems point of view, this makes a great deal more sense. Venous return, if regarded as a flow into the venous system, is too closely coupled to cardiac output to mediate the feedback control of the heart. Indeed, if it were really true, both that increasing venous return leads to an increase in cardiac output and also that increasing cardiac output leads to an increase in venous return, what we would have is not negative but positive feedback, an obviously untenable situation. Venous return is not an appropriate variable to determine cardiac output because it is not an error signal. What matters is not the absolute value of venous return, but its value relative to cardiac output. More precisely, the difference between venous return and cardiac output is a measure of mismatch between the rate of blood entering the great veins and the rate of leaving. If the two are equal, then we are in a steady state, and all is well. It is only when venous return exceeds cardiac output, or cardiac output exceeds venous return, that some action needs to be taken to deal with an unsustainable situation (22).

Any such difference will lead to an accumulating error signal, $\int(\text{VR} - \text{CO})dt$, representing a volume. We suggest this volume might well be called the venous excess (VE), and the rate at which it is growing could be called the venous accumulation rate (VAR). Fig. 1*B* shows how VAR is related to the classic Guytonian diagram; the steady state, when venous return and cardiac output are equal, represents the condition VAR = 0.

Accumulation will result in increased right atrial filling, in turn increasing cardiac output, creating a negative feedback system (Figs. 1*C* and 2*A*). We will then have what a control engineer would call an integral controller, particularly good at eliminating static error in the long term. Thus if blood has accumulated on the venous side, then cardiac output will temporarily exceed venous return to restore the status quo; conversely, after volume depletion, cardiac output will be depressed, venous blood will accumulate, and again the status quo will be restored (Fig. 2*B*).
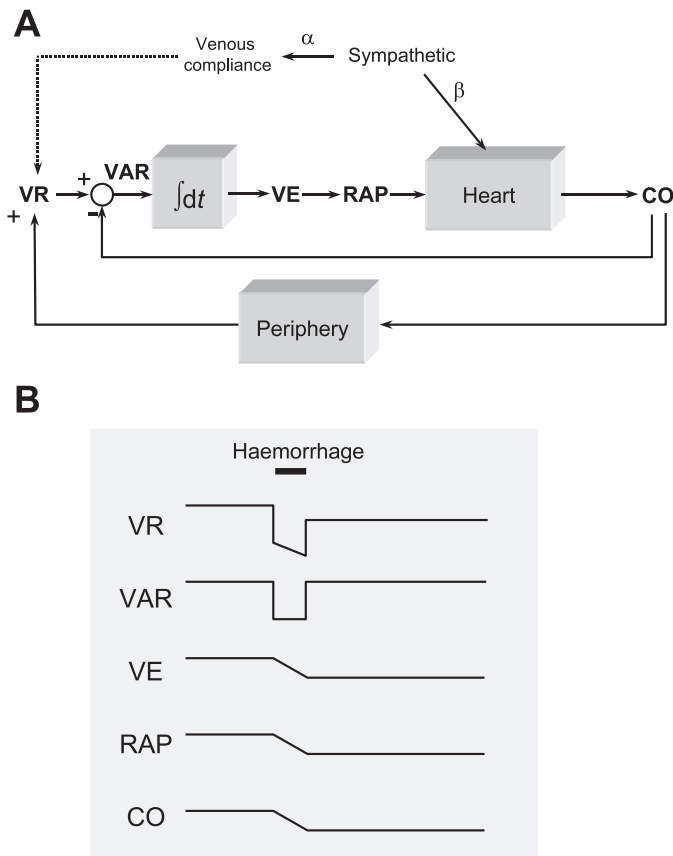
Fig. 2. *A*: formal representation of the feedback system relating VE to RAP and thence to CO. VAR (l/min), the difference between VR (l/min) and CO (l/min), describes the net rate of accumulation of blood at the input to the heart. The integral of VAR represents VE (liters), the cumulative volume that, in combination with venous capacity (Vcap), largely determines RAP (mmHg) and, through the Starling and other mechanisms, increases CO. This negative feedback loop ensures that CO is correctly matched to VR. *B*: behavior in the case of hemorrhage. During the hemorrhage (bar), VR is reduced by the rate of blood loss, resulting in a negative VE and a steady decline in RAP. As a result, CO steadily drops, decreasing VR further, but not VAR. VE, the integral of VAR, thus declines to a lower level that is maintained after the hemorrhage ceases; it falls less than VR because it is offset by the fall in CO. Note that this diagram shows only the venous effects: in addition, the fall in CO will cause a drop in mean arterial pressure (AP) that will accelerate the heart, compensating to some extent for the fall in CO caused by reduced RAP.

As well as stimulating the Frank-Starling mechanism, VE also provides an error signal for other feedback loops. One is the negative feedback resulting from the changes in peripheral venous capacitance that are induced by alterations in VE (24), which alter the distribution of blood between the peripheral and central veins. Other feedback mechanisms that depend on atrial stretch include the release of atrial natriuretic peptide (ANP), which, in the short term, further augments venous capacity and in the longer term reduces blood volume through its actions on the kidney (3, 4). The converse occurs during volume depletion: the error signal, a venous deficit, leads to a diminished cardiac output, reduced stretch receptor activity, and reduced ANP release, all of which serve to reduce the venous deficit. In all of these cases, VE acts as an ideal error signal, feeding back to generate homeostatic effects that result in its own diminution.

Ultimately, although the tasks of the arterial and venous sides of the circulation are different, yet there is a striking

symmetry between the negative feedback systems on the two sides (Fig. 3, Table 1). The arterial system's function is to distribute blood, and its immediate goal of maintaining arterial pressure is a guarantee that any tissue receives the blood that it requests through local vasodilatation. A fall in arterial pressure represents an arterial deficit and generates two main responses: an increase in peripheral resistance through general arteriolar constriction and increased cardiac output, primarily through tachycardia. The function of the venous system, by contrast, is to gather blood. Excessive venous pooling in the periphery, or hemorrhage, will cause venous deficit. In the short term, this triggers venoconstriction, moving blood toward the heart, but a reduction in cardiac output, through a fall in stroke volume and, in the longer term, the restoration of blood volume. It may be helpful to consider in a little more detail the role of VE in the two situations that are usually regarded as being the most significant challenges to circulatory control: exercise and hemorrhage.

During exercise, the cardiac output increases significantly: blood is drawn from the venous system and thrust into the arterial side of the circulation, bolstering arterial blood pressure in the face of reduced peripheral resistance in exercising muscle and augmenting the perfusion of exercising muscles. However, this causes problems on the venous side. First, as the cardiac output increases, the volume of blood on the venous side is reduced, and VE, the signal that drives the Frank-Starling mechanism to increase stroke volume, becomes negative. Second, when cardiac output approaches ~7 l/min, the central venous pressure falls to ~0 mmHg and the central veins collapse, precluding a further rise in cardiac output. To allow the heart to increase the cardiac output further, the circulation must increase its "fullness" (20) and restore the venous volume at the right side of the heart. One way to do so would be salt and water retention by the kidneys, and in the case of hemorrhage and dehydration this is an important homeostatic mechanism; however, this process is clearly far too slow to respond to the requirements of sudden stress and exertion. In the acute setting, the increase in right atrial pressure required to maintain and elevate stroke volume is achieved through the venocon-
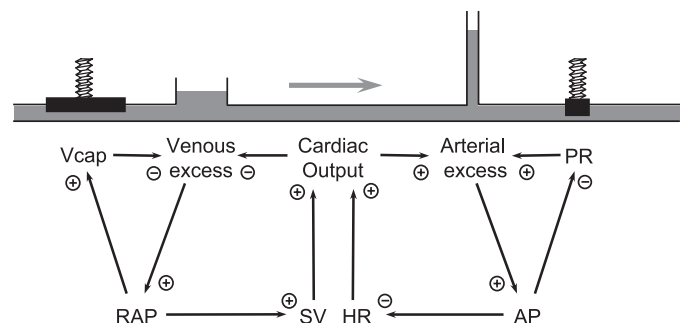

Fig. 3. Similarities and symmetries in the feedback regulation of the arterial and venous sides of the circulation. Arterial excess causes a rise in AP, which, through baroreflexes, causes heart rate (HR) and thus CO to fall and also reduces peripheral resistance (PR). Both of these effects represent negative feedback. VE causes RAP to rise. This leads to increased stroke volume (SV) and CO, while the consequent atrial stretch tends to increase Vcap; again, both of these effects represent negative feedback. In each case, regulation is mediated partly through effects on the heart and partly through changes in vascular tone brought about by reflex and hormonal mechanisms; in each case, both the input and the output to the vascular subsystem are the target of appropriate negative feedback.

Table 1. *The functional parallels between arterial excess and venous excess*

Regulated variable	Arterial excess	Venous excess
Command variables	Cardiac output	Cardiac output
	Peripheral resistance	Venous regional capacitance
	Changes in arterial pressure reflect changes in arterial volume due to imbalance in the rate at which volume enters (a function of cardiac output) and leaves (a function of peripheral resistance) the arterial space.	Changes in venous excess reflect changes in central venous volume due to an imbalance between the rate at which volume enters (a function of factors adjusting regional venous capacitance) and leaves the central veins (a function of cardiac output).
	A steady-state arterial pressure reflects the arterial volume when the rate of volume entry is balanced with the rate of volume exit from the arterial space.	A steady-state central venous pressure reflects the central venous volume when the rate of volume entry is balanced with the rate of volume exit from the central venous space.

strictive effect of muscular contraction and sympathetic activity. The fall in peripheral venous capacitance, manifesting both a drop in the unstressed volume and the wall compliance, increases all vascular pressures (*Eq. 10*) and shifts up to 500 ml of blood from the veins toward the heart (28). As a result, right atrial pressure stabilizes at a new, higher level during exercise (25, 26), with enhanced systolic performance. This mechanism is discussed more fully by Tyberg (32), helpfully illustrated by Gow's piston model (5), who memorably sums it up: "as the veins constrict, the heart tends to expand and vice versa."

In hemorrhage, there is a direct loss of venous volume as blood is lost from the vasculature. Further loss of venous volume occurs as the drop in right atrial pressure, and thus stroke volume causes arterial pressure to fall, stimulating an increase in heart rate (among other things) that helps restore cardiac output by drawing blood from the venous side. As the output exceeds the input, a venous deficit accrues this error signal acting to lower stroke volume (through reduced myocardial stretch) and thus slow the loss of venous volume. As with exercise, sympathetic activity, partly stimulated by falling activity from arterial and atrial receptors, will increase venous tone and decrease venous capacitance (23), thus increasing VE by driving blood toward the heart. By increasing right atrial filling, this will help to maintain cardiac output, albeit at a lower level.

Thus feedback control of stroke volume by VE, in conjunction with feedback control of heart rate by arterial deficit, enables a wide range of cardiac output to be achieved in the face of threats posed by exercise and alterations in blood volume.

Finally, it might well be asked why we propose a measure of volume, VE, as the feedback error signal, rather than a pressure, for instance right atrial pressure, conventionally regarded as the main regulator of stroke volume. The reason is not just that it is a direct consequence of the actual underlying error (a difference between venous inflow and outflow), but also that it represents the more fundamental cause of feedback: ultimately it is not in fact pressure that causes the regulatory effects, but the degree of filling and consequent stretch. Transmural pressure, the distending pressure difference across the cardiac chamber wall, determines end-diastolic volume and thus systolic performance, and it is myocardial distension, the change in volume, that stimulates the atrial stretch receptors and ANP release (14, 31). Thus, although pressure and volume are inextricably linked, it is, nevertheless, volume that proves itself to be the more fundamental variable, that directly engages the Frank-Starling mechanism: an isometric increase in chamber pressure will not be associated with an increased stroke volume. There is a parallel here with arterial baroreceptors, which,

although conventionally regarded as signaling pressure, are actually responding to stretch.

CLINICAL UTILITY

As well as fulfilling the criteria required for an ideal feedback signal in cardiovascular homeostasis, from the clinical point of view, VE is evidently a fundamental variable. When the heart cannot cope with it, it creates edema, and it relates directly to the myocardial pathology, in a way that venous return does not. When cardiac function is depressed, commonly as a result of ischemic heart disease or dysrhythmia, VE accumulates. By increasing the stretch of the functional myocardial contractile elements, enhancing the cardiac output, VE mediates an elegant mechanism of negative feedback. As Thomas Young wrote nearly 200 years ago (34), "When the quantity of the blood transmitted by the heart is smaller than in health, the arteries must be contracted . . . and the veins must of course become distended . . . until the blood, which is accumulated in the veins, has sufficient power to urge the heart to a greater exertion . . ." Venous return, on the other hand, falls with decreased cardiac output (although not to the same extent, or else VE would not accumulate) and rises again only with the restitution of cardiac output, precisely what a useful feedback signal would not do. With continued cardiac depression, when right atrial pressure is increased yet further (as the mismatch between the volume of blood presented to the heart and the cardiac output is further augmented by "compensatory" fluid retention and increased blood volume), the resulting excessive myocardial stretch causes a reduction in cardiac function, a decompensation that is easily understood as a consequence of increased VE. Indeed, when clinicians treating heart failure speak of the need to "offload the heart" with nitrates and diuretics, they are, of course, trying to reduce the VE. Trying to explain all this in terms of venous return, students become baffled: why should cardiac failure be associated with increasing volume overload in the context of diminished venous return?

A final benefit of using VE is that, unlike venous return, it is a tangible variable. Changes can be seen immediately with the unaided eye, visible in the jugular vein as the familiar and easily measurable clinical parameter jugular venous pressure, significant in the assessment and management of hemodynamic status.

It can be helpful to visualize some of these causes and effects on a diagram such as that in Fig. 4, with axes representing right atrial pressure and arterial pressure (they could equally have been labeled as VE and arterial excess). At any moment, the state of these cardinal cardiovascular variables is indicated by a single point on the plane, which moves around
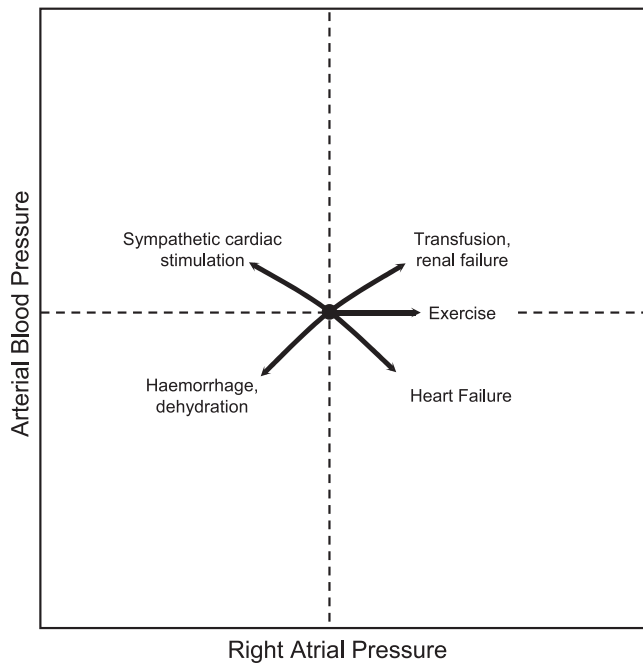
Fig. 4. The effect of various hemodynamic disturbances on both sides of the heart. The figure offers a framework around which to understand both the relationship between the RAP and arterial blood pressure and the mechanisms of the various compensatory mechanisms that come into play when they are challenged. Note that, from a control systems point of view, the axes could have equally been labeled arterial excess and VE.

in response to different conditions. The large central dot corresponds to the heart at rest, and disturbances such as exercise and hemorrhage can be shown as vectors radiating from it in different directions; in general, the directions and magnitudes of the heart's homeostatic responses (intrinsic, hormonal, and neural), are such as to bring the current point back to the center. In the longer term, for example, the renin-angiotensin-aldosterone system elevates both arterial pressure and right atrial pressure in response to hemorrhage and dehydration.

HOW SHOULD WE TEACH IT?

The road of excess leads to the palace of wisdom
(William Blake, Proverbs).

The present teaching in this area is, we would argue, full of muddle and contradiction. Although some may feel that, nevertheless, the classic account is the easiest way for students to grasp what is going on, our experience in small group teaching over some 20 years suggests that this is not so and that it is possible to present the control of the circulation in a way that is simple and intuitive and yet still based on sound physical principles.

A secure way to start is with the core group of five primary circulatory variables. Cardiac output is necessarily the product of stroke volume (SV) and heart rate (HR); arterial pressure is the product of cardiac output and peripheral resistance.

$$CO = SV \cdot HR \qquad (10)$$

$$AP = CO \cdot PR \qquad (11)$$

These relationships are true by definition, so that there is no room for dispute or doubt. As emphasized earlier, these prod-

ucts also represent the causal relationships. Mathematically equivalent formulations such as CO = AP/PR do not express the direction of causality and can lead to such common student errors as thinking that a drop in peripheral resistance will automatically and necessarily result in an increase in cardiac output.

To this almost tautological core we must add some physiology. On the arterial side, we have the overriding negative feedback loop by which the mean arterial pressure is regulated, being sensed by arterial baroreceptors that, in turn, act on brain centers that control both heart rate and general sympathetic vasoconstrictor tone (Fig. 5). In each case, the regulation is by modulation of tonic levels of neural activity: in the one case of the vagal brake on the heart and in the other of tonic vasoconstriction. We can now, for instance, trace the real mechanism by which a fall in resistance does indeed result in increased cardiac output:

$$PR \downarrow \; \rightarrow AP \downarrow \; \rightarrow \text{Baroreceptor activity} \downarrow \; \rightarrow HR \uparrow$$

$$\text{and hence } CO \uparrow$$

To this must then be added the all-important effects of the venous side of the circulation on stroke volume. The Starling mechanism guarantees that the heart pumps out whatever is put into it, that stroke volume is equal to the input of blood to the right atrium. This, in turn, depends on the central venous pressure, modified by heart rate, if this is so high that there is no time during diastole for pressures to equilibrate. Finally, central venous pressure (CVP) depends on blood volume (BV) and on venous capacitance (Vcap), together with some other factors such as gravity and the effect of muscle pumps:

$$(BV \uparrow, VCap \downarrow, \text{inverted posture, exercise}) \text{ all} \rightarrow VE \rightarrow$$

$$CVP \uparrow \; \rightarrow SV \uparrow \; (\text{and perhaps } HR \uparrow \text{ via the Bainbridge effect})$$

To complete the picture, we need to add some more general mechanisms: first, the emergency sympathetic actions such as cardio-acceleration and increased force of contraction, overall vasoconstriction, and venoconstriction, which act globally on the circulation when the blood supply to the brain is threatened; second, the long-term mechanisms regulating blood volume, in particular the hormonal responses to long-term hypotension and to decreased venous volume.
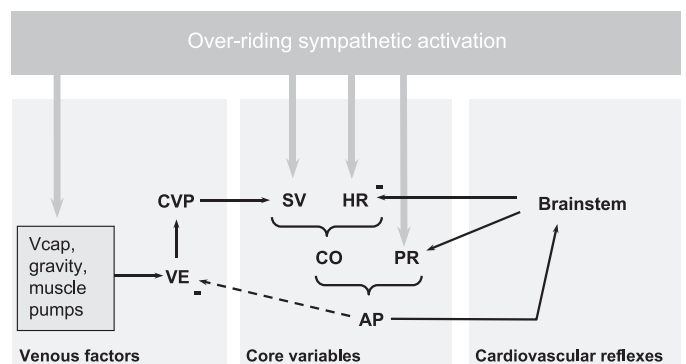

Fig. 5. The functional relationships between the main circulatory variables (VE, Vcap, SV, PR, AP). The relationships among SV, HR, CO, PR, and AP are true by definition; the arrows show physiological regulatory mechanisms, and the dashed line indicates the fact that arterial excess (distension) must cause venous deficit. CVP, central venous pressure.

The finished system (Fig. 5) contains nothing mysterious, no abstract, unmeasurable variables. By systematically working through it, students can very easily work out for themselves the effects of exercise, hemorrhage, and other perturbations. Experience has shown that this approach can be helpful in making these relationships more intuitive and tangible.

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