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Editorial

Giraffes, Siphons, and Starling Resistors

Cerebral Perfusion Pressure Revisited

The fact that we have several definitions for cerebral perfusion pressure (CPP) hints that this apparently simple concept is not so simple. It has become almost axiomatic in our teaching that CPP is the difference between mean arterial pressure (MAP) and central venous pressure (CVP) when CVP is greater than intracranial pressure (ICP):

CPP = MAP – CVP (when CVP > ICP) (Equation 1)

but that CPP becomes the difference between MAP and ICP when ICP is greater than CVP:

CPP = MAP – ICP (when ICP > CVP) (Equation 2)

Now we are reminded of a further option for defining CPP by an article in this issue of *The Journal of Neurosurgical Anesthesiology*. Weyland *et al.* (1) use the difference between MAP and extrapolated critical closing pressure (referred to by the authors as effective downstream pressure or EDP) when EDP is greater than ICP:

CPP = MAP – EDP (when EDP > ICP) (Equation 3)

Before examining this array of options, it is worth noting that each of the definitions above uses a pressure gradient, rather than upstream pressure alone, to define CPP. Otherwise, we could simply define CPP as MAP. It is, in fact, only the choice of which downstream pressure to use that distinguishes one equation from the others. Presumably, we are interested in CPP because it tells us something about cerebral blood flow, which is what really matters; and we have in turn decided that CBF is influenced by downstream, as well as upstream, pressure. The central question is: which downstream pressure is most relevant to flow?

Equation 1 appears to be self-evident, but it may not be terribly useful because the gradient between MAP and CVP defines the perfusion pressure for all systemic vascular beds, not just the cerebral circulation. To know what fraction of the cardiac output is claimed by the brain, we need to know specifically what cerebrovascular resistance is; and that, ironically, is defined as the ratio of pressure gradient to cerebral blood flow. In the absence of determining CBF by a direct, empiric method, the equation isn't of much use; and even then, it is useful only in defining cerebrovascular resistance.

Equation 2 may be more interesting. Here, an intermediate pressure (ICP) replaces the distal pressure (CVP) as the most relevant downstream element in the perfusion gradient. In defining cerebral perfusion pressure this way, however, we are making several physiological assumptions. Primarily, we are assuming the existence and operation of an element called a *Starling resistor*; or, as renamed by Permutt and Riley (2,3) a *vascular waterfall.*

The concept of the vascular waterfall is a milestone in the history of circulatory physiology during the past half-century. Unfortunately, it is no longer widely taught in medical schools, which hampers our ability to critique physiological hypotheses that include vascular waterfalls as a major feature. In order to understand cerebral perfusion pressure equations, however, the concept should be revisited.

Most of us first encountered the terms Starling resistor or vascular waterfall in discussions of West's Zone 2 of the lung (4) so we have modified his schematic (Fig. 1) to refresh old memories.

In essence, Zone 2 describes a situation where blood flows through a collapsible tube that has an external pressure somewhere in the middle of the circuit that is lower than the inlet pressure, but higher than the outlet pressure. In the case of Zone 2 conditions (Fig. 1), the alveolar pressure (P_A) is greater than the pulmonary venous pressure (P_V). As originally described by West (4) blood flow through this zone is responsive to the pressure gradient between arterial pressure (P_a) and P_A, but is completely independent of the far downstream venous pressure P_V.

If we borrow this concept from the lung and apply it to the brain, and use Permutt and Riley's term vascular waterfall, instead of Starling resistor, we might picture the situation as in Figure 2.

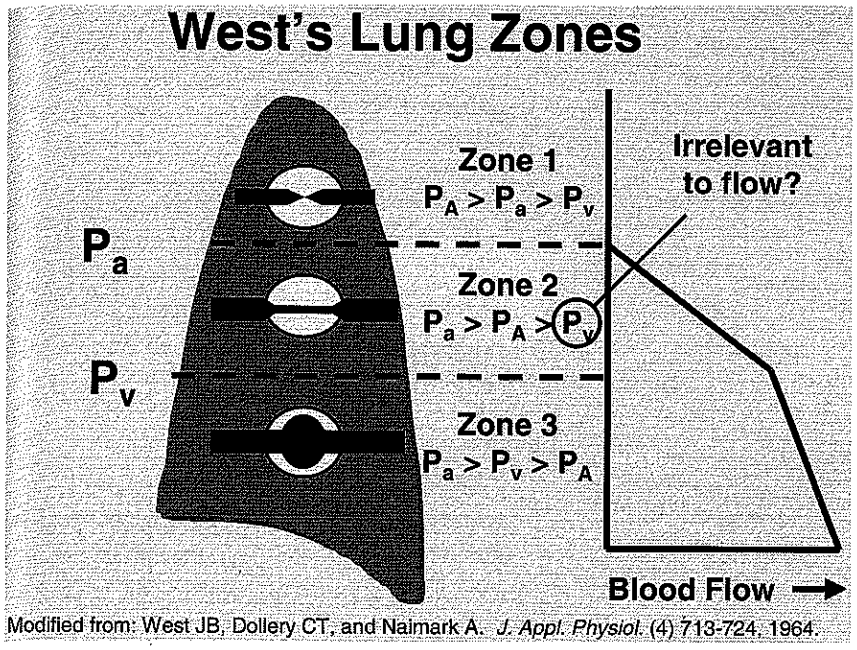

Figure 1.

In the circumstance where ICP is greater than CVP, the vascular waterfall concept holds that cerebral blood flow is unaffected by changes in CVP. As long as CVP remains below ICP, it can rise or fall without affecting cerebral blood flow. This is the direct, visual, implication of using equation 2. The question is: does this scenario actually hold in the cerebral circulation? There are at least reasonable grounds for skepticism.

The concept of the vascular waterfall was initially described by Permutt and Riley to reconcile two older ideas.

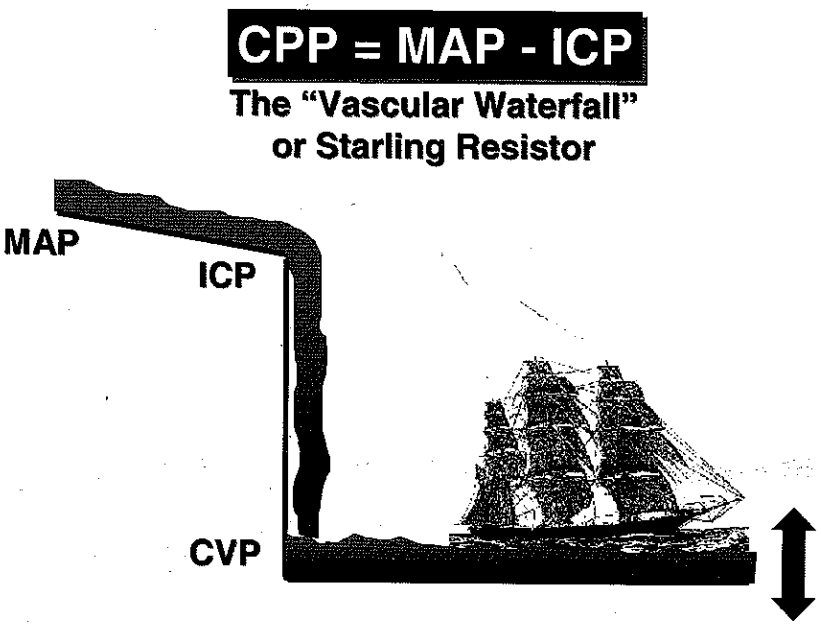

Figure 2.

The first was the simple Starling resistor model, as modified by Holt in 1941 (5). A Starling resistor is any collapsible conduit surrounded in its middle section by an external pressure that is higher than the outlet pressure. In Holt's model, as well as in the later model of Permutt and Riley, the tubing component of the Starling resistor emptied at its outlet into the air. This is an important difference to keep in mind when comparing a classical Starling resistor to the intact circulation. The second principle that the vascular waterfall concept incorporated was Burton's description of critical closing pressure (6). Critical closing pressure is the exact upstream pressure (usually greater than zero), where vessels begin to collapse from their own smooth muscle tone and blood flow falls to zero. It is also called zero flow pressure.

The vascular waterfall concept assumes that a collapsible vessel has to have an internal pressure equal to the external pressure applied to it in order to remain open. It further assumes that an equilibrium is reached where, as flow continues, pressure within the collapsible element falls until the vessel tends to collapse, at which point internal pressure again builds up, opening the vessel for continued flow. If this process sounds very iterative or circular, it is. In Holt's original model, the Starling resistor tubing actually fluttered open and shut within a certain range of outlet pressures. Similarly, when blood is aspirated from a collapsible vein into a syringe, at a certain degree of suction, the vein can be felt to flutter open and closed. With less suction, the vein remains open; and with more suction, it remains closed by the strong vacuum. This is just another example of a Starling resistor. The chief difference between a vascular waterfall and a Starling resistor is that, in the waterfall, it is active vessel wall tone rather than external pressure that causes a tendency to collapse. For our purposes, the importance of either concept is that they appear to lend respectability to the counterintuitive assertion that a far downstream pressure (CVP) can be neglected in defining a perfusion gradient.

It is interesting to note, however, that in both Holt's original model, as well as in our vein aspiration example, flow through the collapsible tubing is not completely isolated from downstream pressure. In either case, flow occurred only during the fluttering phase of the variable pressure gradient between upstream, intermediate, and downstream pressures. If the downstream pressure is reduced too far, the conduit collapses and no flow occurs. Ironically, this feature of the models reinforces, rather than refutes, the role of far downstream pressure, and suggests a major difference between a Starling resistor and a real waterfall.

There is another difference between these conceptual models and the intact circulation. In both Holt's model as well as in the physical model of Permutt and Riley's study, the outlet of the circulatory path empties freely into the air, creating a literal waterfall. The intact circulation is different. In any freely flowing systemic circulatory loop, there is a continuous fluid path connecting MAP to CVP. Figure 3 demonstrates the difference between these two conditions.

If the waterfall shown on the left of Figure 3 is enclosed in a conduit that excludes air (as does the circulation), the waterfall is converted to a siphon, like that shown on the right. Waterfalls and siphons have very different hydraulic characteristics, not the least of which is that siphon flow always depends on the downstream pressure (P_3), whereas flow over a waterfall is independent of the pool at the bottom. If we were to define a useful equation for perfusion pressure for the figure on the left, perfusion pressure $= P_1 - P_2$ would suffice. On the other hand, that equation would be misleading for the enclosed conduit on the right since the equation neglects P_3, and P_3 is directly relevant to flow in that case.

It has not, of course, escaped the attention of physiologists who invoke the existence of vascular waterfalls that a waterfall is a counterintuitive concept for a system of closed conduits. It is difficult to imagine how an abrupt pressure discontinuity could exist within a continuous fluid path. In order to reconcile that difficulty, concepts such as hydraulic jumps and supersonic-to-subsonic flow velocity transitions have been borrowed from hydraulic engineering and applied to the circulation (7). It is far from clear, however, that such elaborate mechanisms can or do operate within the cerebral circulation.

Similarly, if we look for simple empiric demonstrations of a waterfall effect in the cerebral circulation, the literature is wanting. References to Starling resistors or vascular waterfalls within the cerebral circulation cite the original model of Permutt and Riley as well as an empiric study by Luce *et al.* (8). As we've already seen, however, the model of Permutt and Riley relies upon an air interface that does not exist in the intact cerebral circulation. Ironically, the study by Luce *et al.* clearly demonstrates a backward deflection of pressure changes from the sagittal sinus into the cortical veins when the pressure was abruptly increased or decreased at the sagittal sinus. This observation is inconsistent with a waterfall model, but consistent with a siphon model. The fact that the pressure changed more in the superior vena cava than in the cortical veins only points to a differential compliance between these two sites.

Another point of confusion regarding the existence of

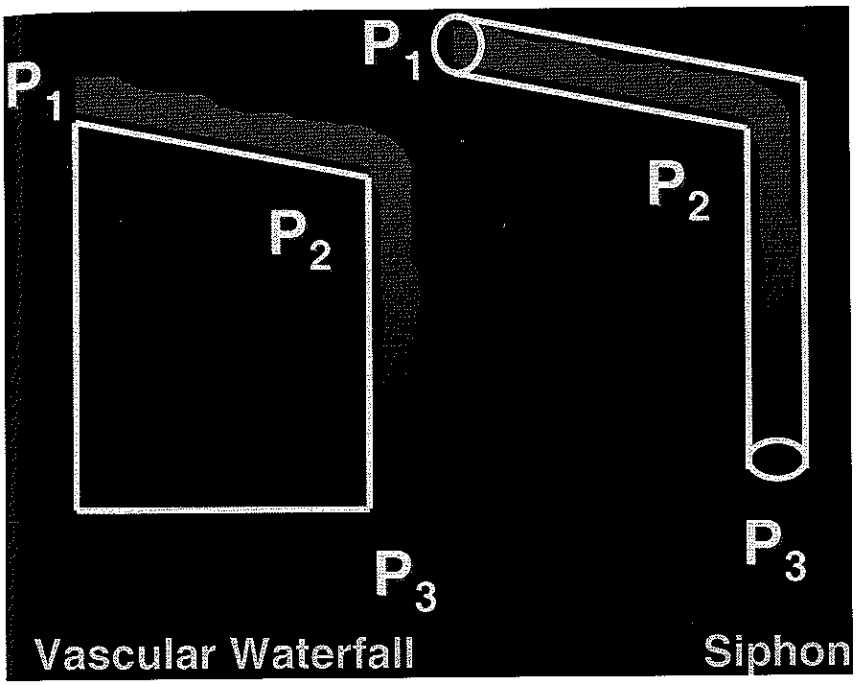

Figure 3.

vascular waterfalls is their presumed location. The present study by Weyland *et al.* uses an elegant and reproducible technique for determining critical closing pressure in the cerebral circulation by extrapolating radial artery pressure and middle cerebral artery flow velocity fall-off during diastole to the zero-flow intercept. Because the estimated critical closing pressures varied inversely with $PaCO_2$, the authors concluded that CO_2-responsive arterioles were the site of critical closure. As with other studies that examined critical closing pressure in other vascular beds, the authors postulated the existence of a Starling resistor at the level of the arterioles. This Starling resistor is assumed to exist in series with a venous Starling resistor that responds to ICP, rather than arteriolar tone.

Since the existence, and site, of presumed Starling resistors or vascular waterfalls plays directly into our concept of cerebral perfusion pressure, it is important to restate the caveat that it is not unanimously accepted that they even exist to any significant degree in the cerebral circulation (9). Pressure measurements taken from the radial artery, coupled to transcranial Doppler studies of MCA flow velocity, leave a large inferential gap between estimates of critical closing pressure on the one hand, and the existence of vascular waterfalls on the other. The designation of estimated critical closing pressure as the effective downstream pressure for cerebral perfusion highlights the need to address some of the points of skepticism outlined above.

Any skepticism of the vascular waterfall concept as applied to the brain should not be misconstrued as skepticism about the importance of ICP, vascular tone, or any other intermediate pressure in affecting cerebrovascular resistance. Each of these pressure elements undoubtedly affects resistance and flow; the use of Equation 1 fully accommodates that. Instead, the questions asked above are aimed at Equations 2 and 3; and at the implicit assumption that downstream pressure (CVP) does not matter when an intermediate pressure rises.

Application to Monitoring

Is this discussion of definitions regarding cerebral perfusion pressure just a matter of semantics? In at least one scenario, it is not. When we monitor patients in the sitting position, our definition of cerebral perfusion pressure takes on a very practical importance. To see what the implications are, consider two approaches to monitoring arterial pressure when the head is elevated. If we adopt Equation 1 as our definition of cerebral perfusion pressure, then CPP will not be affected by body position, and there is no point in raising the transducer to the level of the cranium. On the other hand, if we assume that a vascular waterfall exists in the cerebral circulation, then the local

(transmural) pressure at the edge of the waterfall defines the relevant downstream pressure for cerebral perfusion, and this perfusion pressure gradient will be affected by body position.

The practice of raising the arterial pressure transducer to the level of the brain during sitting craniotomies begs an important question regarding the difference between transmural pressure and perfusion pressure. Raising the transducer will estimate the change in transmural pressure at any point in the circulation that has also been raised to the same height as the transducer. In contrast, raising the transducer does not, and cannot, compensate for, or reflect, the unchanged cerebral perfusion pressure across that circulatory bed.

Whatever our prejudice about the existence of Starling resistors and vascular waterfalls in the cerebral circulation; most would agree that, in the absence of elevated intracranial pressure, cerebral perfusion pressure is defined as the difference between MAP and CVP (Equation 1). CPP includes no term for head position, nor should it. A closed fluid path that begins and ends at the same height (such as the cerebral circulation, which begins and ends at the level of the heart) is gravitationally balanced between the arterial and venous blood columns, no matter how varied the diameter or complex the route between the beginning and end of the circulatory path.

This principle is demonstrated every day by the observation of flow through intravenous tubing. The only defining variables for saline flow through IV tubing are the intrinsic resistance of the tubing/angiocatheter system, and the height of the saline bag relative to the patient. The route of the tubing, whether looped down to the floor or up over the IV pole before reaching the patient, is irrelevant to flow. That is because there is just as much uphill fluid column as downhill fluid column once the relative heights of saline bag and patient are subtracted.

The situation is the same for circulatory paths. When the route of a fluid path between two points at the same height changes, the profile of transmural pressure within that tubing will also change, but the perfusion pressure and flow will not change. A visual analogy may help to clarify this point. Imagine that the heart is holding onto the open ends of a circulatory loop that is filled with blood, analogous to a person holding onto the two open ends of a garden hose filled with water. So long as those ends are at the same height, no water will move into or out of either end of the hose, regardless of the route taken by the middle section. The transmural pressure at any given point in the hose will vary with the height of that point, but the perfusion pressure (the difference in pressure between the inlet and outlet of the hose) will not be affected by the path of the hose. The perfusion pressure will remain zero, and no flow will occur.

Now, if water is mechanically pumped through the hose, the flow rate will be affected by the pressure gradient established between the inlet and outlet by the pump (the perfusion pressure), and by the intrinsic resistance of the hose. But still, the flow rate will not be affected by the path of the hose between the two ends. If we were interested in monitoring the perfusion pressure through the hose, there would be no reason to elevate the pressure transducer to the highest point of the circuit. Doing so would only tell us what the fall in transmural pressure is at that point, which is irrelevant to flow.

When this siphon analogy has been made in regard to the cerebral perfusion of the giraffe (10), it has encountered the objections that vascular circuits are collapsible, that they contain venous valves, and that they have varied diameters. The last point is irrelevant, however, because hydrostatic pressure is only affected by the height of a fluid column, not its diameter or total mass. In other words, a thin column of fluid is perfectly capable of counterbalancing a thick one within a siphon. Similarly, the presence of valves is not important to the argument. Even if venous valves, or valve effects, do exist in the jugular veins of giraffes or humans, they open one-way along normal venous drainage and would not prevent the venous column of blood from counterbalancing the arterial.

The more interesting objection is the collapsibility of the cerebral circuit. Two points should be made about that. First, even if part or all of the cerebral circulation collapsed in the head-up position (which is unlikely in a system that sustains approximately 750 ml/min of blood flow in the steady-state), any open path through the conduit would allow siphon physics to operate in the circuit, regardless of the number of closed parallel circuits. Even in the unlikely event of complete collapse, the elevated arterial column would be sustained by the same finger over the straw effect as pertains in an open siphon. Secondly, the cerebral vessels are contained within a rigid, isovolumic cranium with a fluid interior that is neither very compressible nor very expandable. This makes it unlikely that the majority of cerebral vessels could be collapsed simultaneously by a fall in transmural pressure alone.

A visual description of the difference between transmural pressure and perfusion pressure is highlighted by Figure 4. There are at least three separable components to transmural pressure, neglecting intrinsic vascular tone. *P* denotes the mechanical pressure generated by the heart

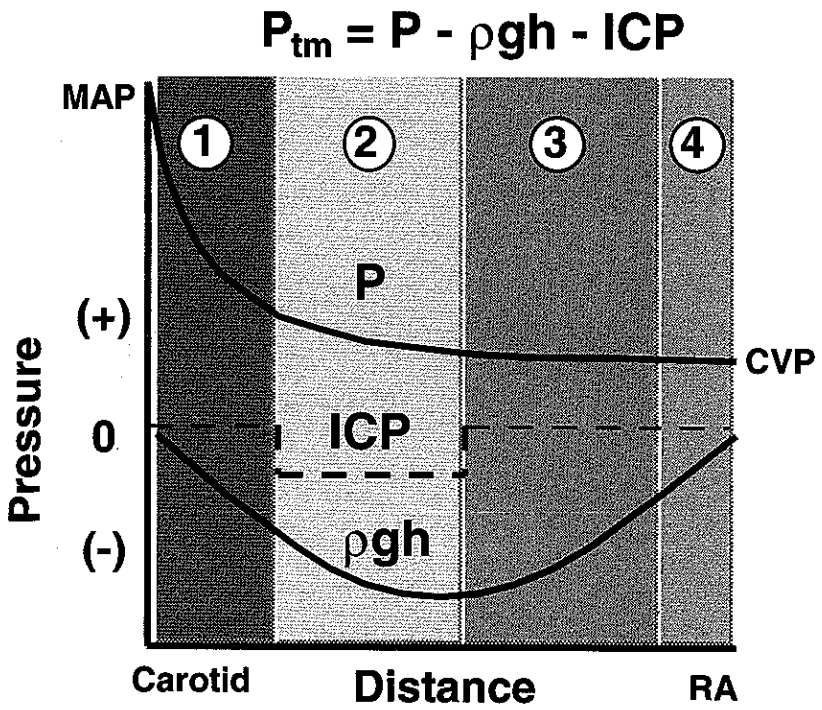

Figure 4.

and decaying throughout the resistance of the cerebral circulation. P starts at MAP and ends at CVP. Between the carotid artery and the right atrium, at least two other intermediate pressures influence local transmural pressure. One is ICP, which operates only within the cranium; and the other is hydrostatic pressure (ρgh, where ρ = density of blood, g = acceleration due to gravity, and h = vertical distance relative to heart level). ρgh begins and ends at zero value relative to the heart. In the sitting position (as depicted in this figure), the ρgh curve reaches its most negative value at the most superior part of the cerebral circulation (approximately the superior sagittal sinus). In a supine patient, the ρgh curve would be flat; and in a head-down patient, it would bow upward. At any point within the cerebral circulation, the local transmural pressure is the simple sum of all three pressures (again, this simple model neglects active vessel tone, but that is not important to the argument about gravitational effects as long as the vessels are patent, and blood flow continues).

There is a simple, empiric test of these concepts. If the cerebral circulation was not gravitationally neutral, then sitting upright should cause a consistent and significant decrease in cerebral blood flow when MAP (measured at the level of the heart) and CVP remain constant. No such effect is evident. In fact, CBF has been observed to remain unchanged (11); to decrease only modestly (12); and even to increase (13) in the sitting position; which, taken together, is consistent with a siphon model.

The practice of raising the transducer appears to be predicated on a model where the heart is assumed to simply lift blood up to the elevated brain without a corresponding and equivalent venous return limb. In a closed-loop system during steady state flow, however, there is a continuous and vertically balanced fluid column, and no

net work is performed against the effects of gravity. This principle was summarized almost three decades ago by the circulatory physiologist A. C. Burton when he wrote: "It is no harder, in the circulation, for blood to flow uphill than downhill (14)." The apparent discrepancy between Burton's statement and our practice of raising arterial pressure transducers when the head is elevated may be because of a confusion of transmural pressure for perfusion pressure; the two are not the same.

It was A. C. Burton who first described critical closing pressure, thus prompting Permutt and Riley's later development of the concept of the vascular waterfall. Ironically, Burton was one of the few physiologists to appreciate the gravitational neutrality of circulatory loops; a concept that depends on the absence of vascular waterfalls in the cerebral circulation, and that gives full due to the effects of the downstream venous component of the circulation. Given that, perhaps it's safe to say that Burton would have favored the first equation: CPP = MAP – CVP.

There is a single concept that unifies the works cited above; that addresses the skepticism raised about the application of Starling resistors and vascular waterfalls to the cerebral circulation; and that cautions against equations for cerebral perfusion pressure that neglect CVP. It is the principle of the siphon.

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