Far from the Madding Crowd:
Assessing volume changes away from the noise of the heart

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The Challenge of Volume Assessment during Neurosurgery

For this discussion, we will divide neurosurgery into two broad categories: craniotomy and complex spine surgery. Craniotomies present several obstacles to our accurate assessment of volume status. The frequent use of diuretics (mannitol and/or furosemide) makes urine output an unreliable guide to hydration. Difficulty in accounting for blood loss into the surgical head drapes hampers estimates of total blood loss. Manipulation of blood pressure (as during aneurysm clipping or in patients with elevated ICP) render arterial blood pressure and heart rate less reliable as guides to volume status, particularly if β-blockers are used. In the case of complex spine surgery (multi-level, tumor, and/or spinal instrumentation surgery), prone positioning itself affects heart rate, blood pressure, and urine output - even without corresponding changes in blood volume. Spine surgery also presents the anesthesiologist with a remarkable range of blood losses to contend with, varying from trivial to multiple liters. Finally, the recent growth of intraoperative cell-salvage and pheresis techniques has complicated our estimates of surgical blood loss, even while aiding our ability to avoid non-autologous transfusion.

Debate continues as to indications for central venous pressure (CVP) monitoring in neurosurgical patients, with some practitioners suggesting that it should be standard of care for craniotomy patients; and others arguing that the risks and costs of widespread CVP placement outweigh the benefits for many or even most craniotomy patients. In this review, we will revisit the physiology of circulating blood volume in both normal and pathophysiologic states. This will allow our discussion of monitoring techniques to proceed from physiological principles rather than from individual prejudice and practice alone. As with other debates about monitoring in anesthesiology, we are handicapped by the virtual impossibility of demonstrating a difference in patient outcome between alternative techniques. The lack of an “outcome-based medicine” approach, however, does not mean that monitoring decisions are without consequence for our patients. In the case of CVP placement, the extra time, cost, and iatrogenic complications associated with the monitor are well described; and any possibility of an effective replacement carries significant implications for improved patient safety, whether or not that improvement is easily demonstrable in outcome studies.

The Physiology of Volume Assessment

In answer to the question, “what is optimal blood volume?”, we need to answer several other questions first. For example, we need to know how big the patient is. Certainly,

“optimal volume” for a 100-kg adult is not the same as for a 20-kg child. Neither is optimal volume for a non-pregnant woman the same as for the same patient who is pregnant and at term. If we answer the question empirically by simply measuring average blood volume as a function of age, sex, weight, height, pregnancy status (for example, by observing that 70 ml/kg is an optimal blood volume for a middle-aged male because most healthy middle-aged males have about 70 ml/kg blood volume), we are only part way to answering the original question. The next question becomes, “what *purpose* does blood volume serve, and *why* is 70 ml/kg optimal?”

There are several potential answers to that question, and each of them moves the discussion beyond volume alone. For example, oxygen carrying capacity is a function of total blood volume. So is the body’s efficiency in removing carbon dioxide and metabolic wastes a function of blood volume. Those two points, taken in isolation, would suggest that “the more blood volume the better,” however; without an obvious end in sight. The next answer might include considerations of circulatory efficiency as a function of total blood volume. After all, the circulatory system is just that – a conveyer belt, or convective transport system, and there must be some optimal blood volume where cardiac output is maximized. Too little volume, and the heart is “pumping empty” without an adequate priming volume (pre-load); but too much volume, and the capillaries leak while the heart fails from volume overload.

In the practice of neuroanesthesia, most of us have seen an intraoperative aneurysm rupture with massive, sudden blood loss. Unless the circulating blood volume is restored quickly to maintain an adequate “stressed blood volume” (which we will define soon), it doesn’t matter what the heart rate , inotropy, or vascular tone is – the patient is at risk of cardiac arrest because the heart has inadequate volume to work with. Similarly, when we are presented with a patient in heart failure, we know the dangers of over-hydration, and we can assume that the cardiovascular system has on board too much of a good thing.

These examples may provide an intuitive sense that optimal blood volume lies somewhere between an empty heart on the one hand, and bulging capillaries on the other. We might also conclude that, between these extremes, it is probably better to have more that less volume. The brain places special demands on what we consider “optimal volume,” however, because of its tendency toward edema formation, particularly when the blood-brain barrier (BBB) is disrupted, or in the aftermath of traumatic head injury. We might reach a provisional conclusion, then, that “optimal volume lies somewhere between an empty heart and bulging capillaries, more towards bulging capillaries, but short of brain edema formation, especially after head injury.” That is a pretty awkward and vague guideline; obviously, so let’s try to put some numbers to it.

First of all, it may be clear by now that *volume* may not be the easiest type of number to use in discussing hydration status. For one thing, absolute blood volume is difficult to measure. For another thing, even if we could easily measure absolute blood volume, it might not be as useful to us as *pressur*e. From the point of view of the heart, total blood

volume is detectable as a change in pressure. When we place a patient on cardiopulmonary bypass, for example, the volume of the reservoir is added to the total intravascular volume, but the heart doesn't "know" that the total circulating blood volume has changed, and only detects the pre-load, or pressure, that it is presented with.

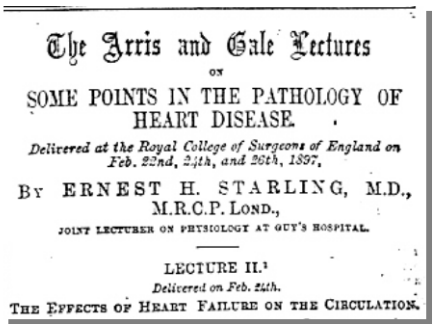
What seems to matter to the heart, and to the capillaries, is the *ratio* of blood volume to total vascular compliance. Specifically, what matters is the ratio of *"stressed blood volum*e" to vascular compliance. Stressed blood volume is simply the amount of blood volume above the "unstressed," or "priming" blood volume. The unstressed blood volume in an adult is about 2 liters. That is the amount of blood necessary to even begin to stretch the vessel walls of the cardiovascular system so that pressure begins to rise above zero. That is also the amount of blood volume below which the heart begins to "pump empty," and is no longer able to generate a cardiac output or maintain an elevated arterial blood pressure. Once blood volume rises above the unstressed volume of the cardiovascular system, the venous pressure begins to rise as a function of the compliance curve of the blood vessels. This important ratio of stressed blood volume to vascular compliance is called "mean systemic pressure" (P_{ms}), or "mean circulatory pressure":

$$\mathbf{P_{ms} = (V - V_o) / C} \quad \textit{(Equation 1)}$$

where V is total blood volume, V_o is unstressed blood volume, and C is the overall compliance of the cardiovascular system (a function mainly of the venous side, since that's where the majority of the blood volume resides).

Mean systemic pressure (P_{ms}) has three important implications for hemodynamic monitoring. First, it is the effective "upstream" pressure that drives venous return, and ultimately, cardiac output. Second, it is the pressure to where all parts of the cardiovascular system converge during planned circulatory arrest. Third, it is theoretically the single best pressure for us to use in estimating a patient's hydration status. Before examining each of these facets of P_{ms}, it should be pointed out that its normal value is about 15 mmHg in humans, and 7 – 15 mmHg in dogs. After we look at each of the three implications cited above, we will visit a new monitoring strategy that may allow us to estimate P_{ms} during neurosurgery in a safe and simple way, and will compare that monitoring strategy to CVP measurement.

When we do planned circulatory arrest cases under deep hypothermia for the repair of giant cerebral aneurysms, we are achieving the same kind of convergent arrest pressure that was first described over 100 years ago by Sir Ernest Starling. The figure below represents a re-plotting of Starling's original data, which he demonstrated by an incremental infusion of oil into the pericardium of anesthetized dogs. As the cardiac tamponade progressed, all measured vascular pressures began to converge until the point of cardiac arrest, where no pressure gradients could be maintained within the cardiovascular system. Just as the equation for P_{ms} above would predict, the resulting pressure was not zero. Instead, it was the result of the ratio of stressed blood volume to vascular compliance, and was measured at about 15 mmHg.



The Arris and Gale Lectures
ON
SOME POINTS IN THE PATHOLOGY OF HEART DISEASE.

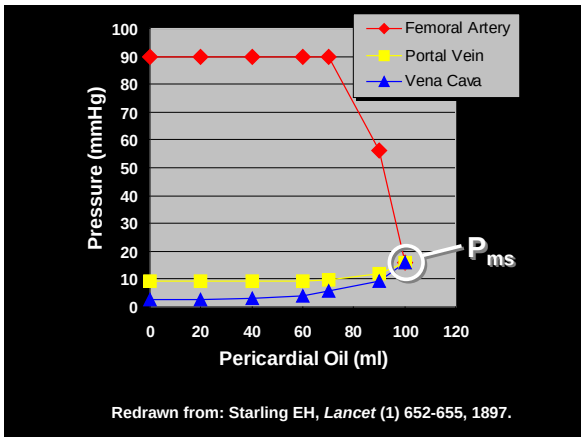
Delivered at the Royal College of Surgeons of England on Feb. 22nd, 24th, and 26th, 1897.

BY ERNEST H. STARLING, M.D., M.R.C.P. LOND.,
JOINT LECTURER ON PHYSIOLOGY AT GUY'S HOSPITAL.

LECTURE II.[1]
Delivered on Feb. 24th.

THE EFFECTS OF HEART FAILURE ON THE CIRCULATION.

The Lancet (1) 652-655, 1897



A half-century after Starling's experiments, the physiologist Arthur Guyton made further use of P_{ms} by pointing out that it represented the effective upstream pressure for venous return, and ultimately, of cardiac output. Like Starling before him, Guyton used an anesthetized dog model, and he opined that we might never know what P_{ms} is in humans because of the obvious danger of circulatory arrest. Because of the advent of modern cardiopulmonary bypass and hypothermic techniques, however, we are now able to achieve circulatory arrest in patients, then return them safely from the arrest phase. When we perform planned circulatory arrest, we see a pattern of pressure convergence that is identical to that of Starling's and Guyton's experiments, and with a typical value for P_{ms} of approximately 15 mmHg.

Why is P_{ms} so important to venous return, and to cardiac output? The answer to that question takes us back to Arthur Guyton's experiments, and to his pioneering concept of "venous return curves." It also takes us back, however, to a countervailing opinion offered by another prominent circulatory physiologist – Matthew Levy. We will first give a brief description of Guyton's analysis of venous return; then visit Levy's contrasting view; and finally, explain how Levy's view of the circulatory system plays into our renewed interest in developing a different hemodynamic monitoring strategy.

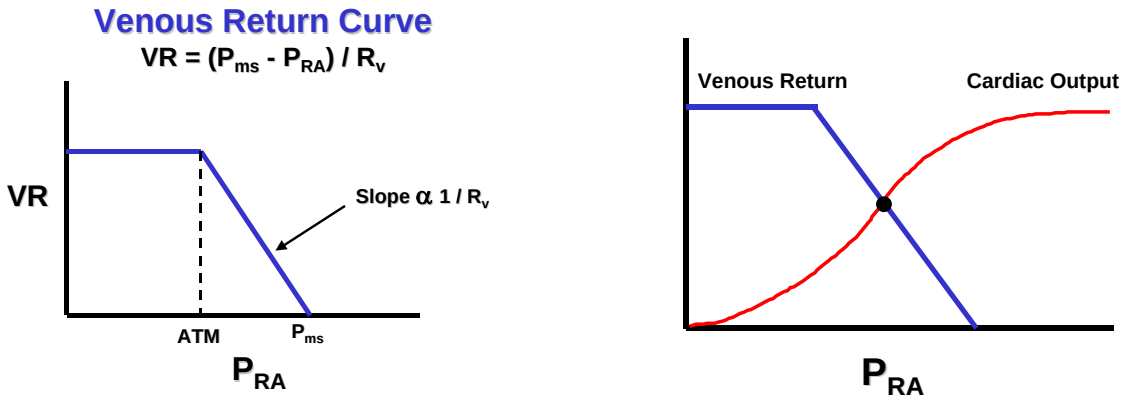
First, the current model: Guyton explored a very simple relationship between P_{ms}, right atrial pressure ($P_{RA,}$ or, for our purposes, CVP), and venous return (VR). In the steady state, venous return is equivalent to cardiac output, so he reasoned that the determinants of venous return were ultimately the determinants of cardiac output. Guyton used a hydraulic analogue of Ohm's law of electricity, which relates a pressure gradient to a resistance and a flow:

$$\mathbf{VR = (P_{ms} - P_{RA}) / RV} \qquad \textit{(Equation 2)}$$

Where RV = resistance to venous return. By this relationship, P_{ms} is assumed to be the "upstream" pressure driving venous return. Why did Guyton pick P_{ms} as the upstream pressure in the gradient for venous return? Why not arterial pressure? The reason is empiric. In an animal model where a dog is placed on cardiac bypass, the easiest way

to discover the upstream driving pressure is to raise the downstream pressure (right atrial pressure, P_{RA}) until flow stops. When Guyton did this, he could only raise P_{RA} to the level of mean systemic pressure before the cardiac bypass pump began to run empty (from lack of venous return) and failed. This happened long before P_{RA} got to arterial pressure; but instead, happened when PRA approached about 15 mmHg. In fact, as PRA rose, venous return fell, cardiac output fell, and arterial pressure fell. At complete circulatory failure, all pressures converged to P_{ms}. Again, this result could have been predicted based on Starling's observations.

Other investigators who have attempted to study circulatory dynamics by raising P_{RA} alone have rediscovered the same phenomenon: *"what goes around comes around*," – it is impossible to raise P_{RA} without simultaneously impeding venous return; and therefore, cardiac output and arterial pressure. The circulatory system is just that – a circle – and no one element of the circle can be studied in complete isolation from the rest of the circuit without a domino effect occurring. For example, when the physiologist Richard Traystman and his colleagues attempted to study the autoregulation of cerebral blood flow by raising CVP, they discovered that it was necessary to first give a massive volume load to the dogs in their model before raising P_{RA} by mechanical means. Unless they raised total volume first (and therefore, P_{ms}), they could only elevate P_{RA} to levels approaching a normal mean systemic pressure before the bypass preparation failed.

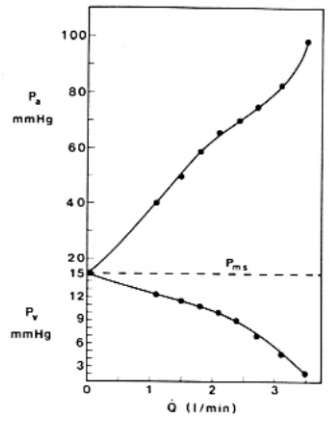


Guyton attempted to incorporate the determinants of venous return, and the interdependency of venous return and cardiac output, into a simple graphical description of the circulatory system. To do this, he simply superimposed a "venous return curve," which relates venous return to P_{RA} (with P_{RA} being the independent variable, or "cause," and venous return the dependent variable, or "effect") with a "cardiac function curve," which relates P_{RA} to cardiac output. In the venous return curve depicted on the left, when P_{RA} is equal to P_{ms}, venous return is zero. As P_{RA} is lowered below P_{ms}, venous return increases until an upper limit is reached, where P_{RA} falls below atmospheric pressure (ATM) and the thoracic veins begin to collapse, impeding further increase of venous return. The graph at the right depicts the superimposition of a cardiac function curve on top of a venous return curve. Guyton reasoned that the unique intersection of those two curves would represent the true cardiac output – the

compromise reached between P_{RA} acting as the impediment to venous return on the one hand; and as the preload for increased cardiac output on the other:

This was a very clever way of dealing with the apparently paradoxical roles of P_{RA}, but it begged an important question about cause-and-effect; that is, about the assignment of independent and dependent variables. Matthew Levy took issue with Guyton's assumption that venous return could be viewed as a flow that results from a pressure gradient; rather than the other way around. Levy reasoned that the primary variable was cardiac action generating flow, and that a pressure gradient was the *result* of, not the *cause*, of venous return.

We are so often taught that "pressure gradients cause flow" that we are inclined to believe it without question. However, pressure is not energy until coupled to a volume change (that is, a flow); and without energy, no flow can occur. In other words, a thermodynamic, as well as physiologic, case can be made that flow comes first, and that it is the cause, not the effect, of a pressure gradient across a resistance.



From: Levy, Matthew N.
Circulation Research
(44) 739-747, 1979

Pressure

Flow

The data above may help to clarify this point. It depicts a very simple experiment: A dog was placed on cardiopulmonary bypass, and the perfusion pump was under the direct control of the experimenter. That is, the flow rate (Q) was simply dialed in, and the resulting venous (P_v) and arterial (P_a) pressures were measured. When no flow occurred (the pump was set to zero), the resulting venous and arterial pressures were at the level of P_{ms} (that is, at about 15 mmHg, just as Starling had demonstrated 100 years ago). As the flow rate increased, the arterial pressure rose, and the venous pressure fell. In this simple experiment, it is hard to argue that the flow was anything other than the *cause*, and the pressure gradient the *effect*. In other words, Levy questioned the assertion that a "gradient for venous return" was the cause of, rather than the effect of, venous return. Perhaps it would be more accurate to call it the "gradient *of* venous return" rather than the "gradient *for* venous return."

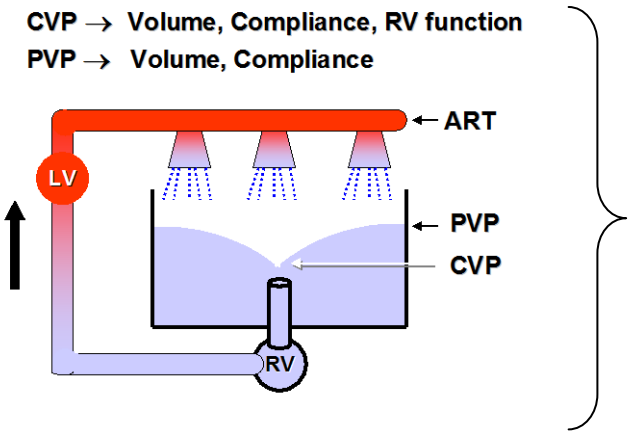
Why should this chicken-or-egg question matter? It matters because if we are to make sense out of what CVP means physiologically; or if we are to challenge CVP with a rival monitor of relative volume status, then we should be obliged to reconsider what CVP actually tells us. Taking stock of all that we've just visited above, a reasonable provisional definition of CVP might be as follows:

CVP represents a local distortion of mean systemic pressure caused by the right heart.

Viewed this way, the absolute value of CVP will then be a function of three variables: 1) stressed blood volume; 2) venous compliance; and 3) right heart function (suction). If this definition is accurate, we might question how good CVP is as a monitor of "optimal blood volume." If CVP represented the ratio of blood volume to venous capacitance only, then it would be a "pure" measure of relative volume status. Since CVP is also influenced by right heart suction (which depresses local venous pressure below Pms), it is not so "pure."

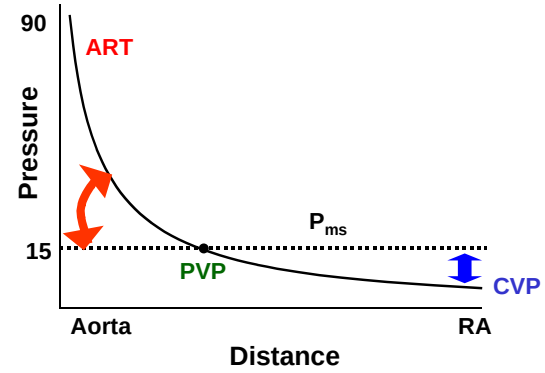
What about P_{ms} as an estimate of optimal blood volume? The theoretical advantage of P_{ms} is its simplicity. P_{ms} represents only the ratio of volume to compliance, which is what we're really interested in when we consider hydration status. It includes no term for cardiac function, and is not influenced or affected by cardiac function. In fact, as we've seen, P_{ms} is determined in the *absence* of cardiac function at cardiac arrest. Acutely, P_{ms} will remain the same during normal cardiac function, during depressed cardiac function, or even at cardiac arrest. During chronic heart failure, compensatory mechanisms increase blood volume in order to maintain cardiac output, and P_{ms} will increase. That is why chronic, but not acute, heart failure results in capillary edema. In a normal patient, capillary pressure is *above* P_{ms} (approximately 25 mmHg compared to 15 mmHg), so acute heart failure will *lower* capillary pressure in the systemic vessels and not result in edema formation. In chronic heart failure, however, blood volume increases, resulting in an increase in P_{ms} to a level at or above normal capillary pressure, and edema occurs. All of this was considered by Starling over a hundred years ago.

The simplified graph below depicts a "systemic pressure decay curve," which demonstrates what happens during circulatory arrest, and highlights the potential advantage of P_{ms} as a volume monitor. Systolic/diastolic pressure fluctuations are not depicted. The heart may be considered as a mechanism to elevate arterial pressure while simultaneously lowering central venous pressures (by translocating blood volume from the central veins to the arteries). This is characteristic of any mechanical pump – pressures are simultaneously raised on one side of the pump while being lowered on the other side. At circulatory arrest, all pressures converge to P_{ms} (dotted line). Note that there is one point on the systemic pressure decay curve where the arrest pressure line intersects with the intact circulation curve. That point is P_{ms}. This is just another way of reiterating that P_{ms} is independent of cardiac function. As blood volume or vascular compliance change, however, the P_{ms} line will move up or down. CVP may be thought of as the result of right heart function *depressing* local pressure, and arterial pressure as the action of the left heart in *raising* local pressure, above P_{ms}.



CVP is measured at the right heart inlet, and is a function of three variables: 1) blood volume, 2) venous compliance, and 3) transient right heart function. PVP reflects only two variables: 1) blood volume, and 2) venous compliance - and is therefore not effected by RV function. During prolonged diastole or during circulatory arrest, CVP rises, ART falls, and PVP remains unchanged as blood volume redistributes from arterial to venous compartments. PVP estimates mean systemic pressure (Pms), which is the value to which all other pressures converge at circulatory arrest, and which is a direct measure of the ratio of total blood volume to vascular compliance. **CVP, in contrast, represents a local distortion of Pms secondary to right heart suction.**

With each systolic contraction, arterial pressure (ART) is elevated above, and CVP is depressed below, Pms. During diastole, ART and CVP begin to converge again towards Pms, but this convergence is interrupted by the next systole. During circulatory arrest, full convergence occurs to Pms. PVP estimates Pms, and therefore, does not change with systole, diastole, or circulatory arrest; but continues to reflect volume regardless of the level of cardiac activity

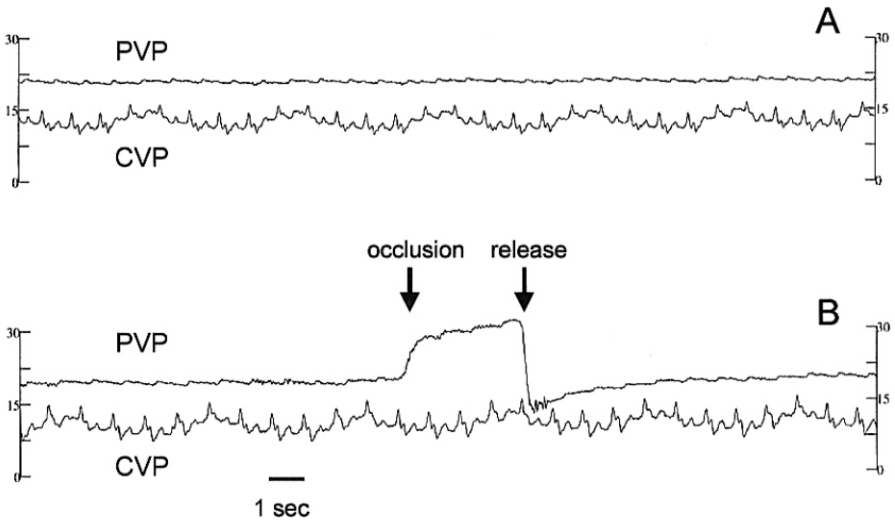


Peripheral venous pressure (PVP) as a clinical monitor of volume status

If we had a way of measuring P_{ms} while the heart was still beating, we could estimate volume status efficiently in neurosurgical, or in any other, patients. One way of achieving the measurement of Pms in normal clinical circumstances is to use the crossover point between the circulatory arrest and normal systemic pressure decay curves. If we could measure pressure somewhere in the systemic circulation where that crossover occurs, then we could estimate P_{ms} without stopping the heart. Physiologists have surmised that the crossover point occurs somewhere in the post-capillary venules or veins, so we have looked at peripheral venous pressure (PVP) in both neurosurgical patients and in an anesthetized dog model.

One potential objection to measuring PVP is that venous valves might intervene between the measurement site and the central circulation. During steady-state flow, however, venous valves remain open, and fluid continuity exists between peripheral veins and the heart. For the purposes of measuring pressure gradients, “an open valve is no valve,” unless a remarkable stenosis occurs at the valve site. Venous pressure gradients are also modest, so resistance and flow characteristics are relatively unimportant when compared to the arteries or the left heart. We also know that

intravenous drugs reach the central circulation quickly, without being sequestered in a hand, arm, or foot site. PVP waveforms also reveal a modest respiratory variation, in synchrony with that seen in CVP waveforms. Finally, distant downstream limb occlusion and release results in simultaneous pressure changes at the PVP measurement site. Taken together, these findings suggest that PVP readings are not affected by the presence of venous valves.

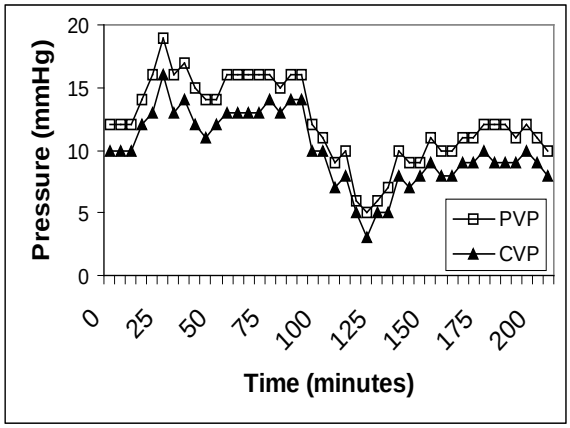


PVP and CVP waveforms (A), with transient proximal arm occlusion and release (B)

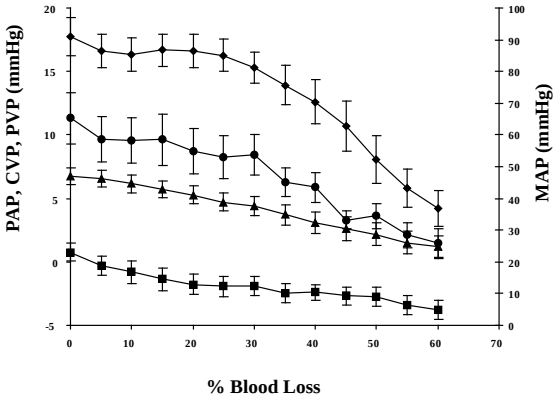
A second potential objection to measuring PVP is that the measurement might reflect local, rather than systemic, pressures. For example, temperature changes in an extremity might cause venoconstriction or venodilation that would prejudice PVP measurements in that extremity when compared to other sites. That objection appears to have been answered on three separate grounds. First, direct, simultaneous comparisons between PVP measurement sites in opposite hands, arms, or even foot sites reveal no significant differences. Second, PVP trend measurements from any peripheral site demonstrate a robust correlation to CVP trends, suggesting that the two are communicating, rather than discontinuous (figure below, left – mean PVP levels in 15 patients across 1,026 measurements are 13 mmHg, compared to 10 mmHg for CVP. This includes supine, lateral, and prone positioning for either craniotomy or complex spine surgery. When one parameter changes, so does the other, in synchrony). Finally, on a theoretical level, all systemic veins ultimately converge at the right atrium, and that pressure convergence at a common outlet, combined with relatively low pressures and slow flow velocities prior to the common outlet, provide for a “pressure equilibration” between even widely separated systemic veins.

A critical question remains about the validity of PVP as a reflection of actual blood volume. In order to begin to answer that question, we have made careful measurements

of PVP and CVP in an anesthetized dog model, with incremental blood volume addition or removal. The correlation of PVP with hemorrhage is essentially linear (r = -0.997), even down to a removal of 60% of estimated total blood volume (figure below, right: PVP values represented as solid triangles).



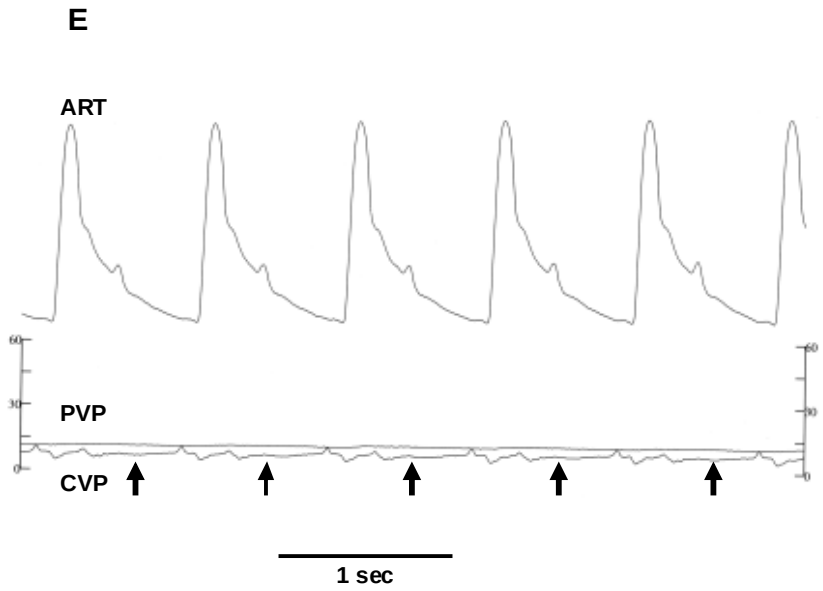
Data from a craniotomy patient demonstrating Simultaneous PVP and CVP measurements.



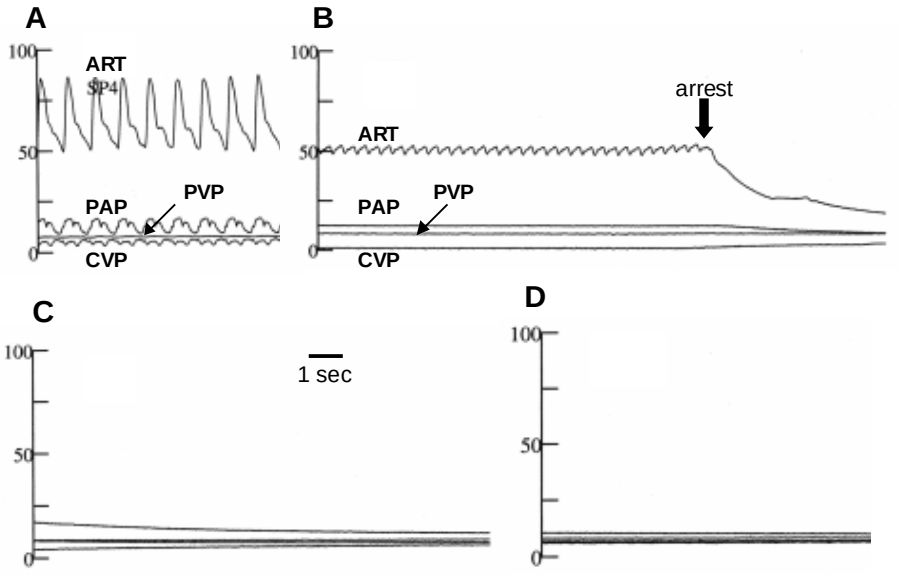
Data from controlled hemorrhage in 16 dogs. PVP values are represented by filled triangles, MAP as diamonds, PAP as circles, and CVP as squares.

Finally, in order to test the hypothesis that PVP estimates Pms in humans, we have made simultaneous measurements of arterial pressure (ART), pulmonary artery pressure (PAP), PVP, and CVP during controlled circulatory arrest in humans (Figure below). These cases demonstrate pressure convergence to PVP, with little or no change in PVP itself, at circulatory arrest. This suggests that PVP can be used to estimate Pms when the heart is functioning. If this observation is confirmed, then the answer to Arthur Guyton's question about the determination of P_{ms} in humans may lie no further away than the measurement of the pressure in simple intravenous lines.

Discussions of hemodynamic monitoring are often handicapped with little outcome data to support what are often very strongly held opinions about efficacy, safety, and clinical indications. This review of PVP is no different, in that it challenges the widespread use of a veritable old monitor with something that is apparently too simple to be true, and that is likely to meet resistance. We hope at least that it will spark a renewed discussion of the underlying physiology and rationale for venous monitoring at *any* distance from the heart, and that it will refresh a historical perspective on hemodynamic monitoring.



Diastolic runoff: ART and CVP begin to converge on PVP, until interrupted by the next atrial contraction and systole.



Data from a controlled circulatory arrest in a patient, demonstrating convergence of pressures to PVP.

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