Phenylephrine and Tangible Bias

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In this issue of *Anesthesia & Analgesia*, Thiele et al.[1,2] define a "tangible bias" as "our tendency to favor what we can see and understand over what we cannot," and argue that the use of pure α agonists such as phenylephrine "is driven by this bias by favoring less important but immediately measurable variables, such as mean arterial blood pressure, over more important but less measurable variables, such as tissue oxygen delivery." This bias unfortunately runs through much of our regular resuscitation practices, and as Thiele et al. demonstrate in their comprehensive reviews, this bias is especially true for the use of phenylephrine, which effectively increases blood pressure but does little for tissue perfusion.

There are perhaps some clinical situations in which phenylephrine might be helpful. Phenylephrine can be lifesaving in hypotensive patients who have dynamic aortic outflow-tract obstruction. It has been shown to increase cardiac filling during postural hypotension[3] and could have a potential use in patients who have an acute loss of α-adrenergic tone. Other recipients for phenylephrine cited by Thiele et al. include patients with decompensated tetralogy of Fallot, women with hypotension undergoing cesarean delivery, and patients with decompensated aortic stenosis. The evidence for this last indication is limited, and there has not been a comparison with the use of norepinephrine; it even has been shown that nitroprusside can be helpful![4] There also might still be a place for anesthetists to carry a syringe of phenylephrine in a pocket to transiently increase the blood pressure to ensure coronary perfusion pressure when arterial pressure rapidly decreases after induction for intubation; a study to prove that point would be very difficult to perform and, based on the review by Thiele et al., I suspect it is less beneficial than the use of norepinephrine.[5] Finally, an old but still likely valid use of phenylephrine boluses is to transiently raise arterial pressure to increase vagal output in someone with a supraventricular tachycardia, especially if the person is already hypotensive. Besides these special situations, there seems to be little value for sustained use of pure α agonists.

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The failure of phenylephrine to increase flow is an excellent example of the distinction between increasing pressure, which we can see, and increasing flow, which we cannot. The reason why it fails to improve flow also provides important insights into the regulation of blood flow in the circulation. To help interpret the empiric data, Thiele et al. present a comprehensive review of the regulation of cardiac output,[1] and although there are many parts of their discussion that I agree with, I also have some fundamental disagreements, and will argue that failure of phenylephrine to increase flow provides support for my view of how the circulation works.

Thiele et al. use an electrical analogy based on Ohm's law to explain the regulation of flow, and start by arguing that the proper formulation of Ohm's law is I (current) equals V (voltage) divided by R (resistance). Accordingly, they argue that cardiac output is determined by arterial pressure divided by vascular resistance, because they believe that the arterial pressure determines total blood flow just as voltage determines the current. Ohm actually wrote his law as V = IR, and in my view, this is the valid form for the circulation. That is, blood pressure is determined by the product of cardiac output and vascular resistance, which are regulated to keep arterial pressure relatively constant.[6,7] The arterial pressure does not determine total flow (cardiac output). Regional blood flows, such as coronary, cerebral, or renal blood flow, are determined by arterial pressure divided by the regional resistance, but the arterial pressure driving the regional flow is determined by the total blood flow and total arterial resistance. Even in regional circulations, changes in resistance regulate flow over a range of arterial pressures.

Part of the problem arises with use of the electrical analogy. In the electrical approach, voltage—the equivalent of the pressure difference—is fixed by an external source, which then is taken to be the equivalent of the energy provided by the heart. However, unlike the electrical analogy, the circulation has an important resting potential energy stored in vessels, even without a contracting heart; puncturing vessels with the heart stopped still leads to blood flow in the system, albeit only temporarily. Although this potential energy seems low, the beating heart can never create a flow in the system that is higher than that produced by this elastic recoil pressure.[8]

The actual blood flow in the body is determined by the intersection of 2 functions,[6,9] which are both sensitive to volume. They are cardiac function, which gives the change in output for a given end-diastolic volume at a constant heart rate, constant afterload, and constant contractility, as

defined by Frank and Starling, and second, the return function, which is defined by the stressed volume, which stretches compliant vessel walls and produces an elastic recoil pressure, the drainage characteristics of these vessels, and the downstream pressure, which is at the right atrium. The bulk of stressed volume, almost 70% of the total, is in small venules and veins, for this region has compliance that is 30 to 40 times that of other vessels in the body. Because total compliance of a system is the sum of the individual compliances in series, and the compliance of venules and veins is so much larger than that of the remainder of the body, lumping all the compliance in the body in this one region makes the overall analysis much simpler and adds only a small error in the assessment of the regulation of cardiac output under most conditions. The pressure and volume in this compliant region thus are the primary determinants of the elastic recoil pressure for the circulation and the potential energy driving blood back to the heart, which I call the return function. Flow does not occur unless the heart lowers the pressure downstream from the veins and venules. Actual flow around the circulation is thus determined by the intersection of cardiac and return functions. The second important role of the heart is a restorative function, because the heart puts the blood back into the venules and veins.

The key role of blood volume in the determination of the elastic recoil pressure, a major determinant of flow,[10] is not present in electrical models, although they do include the equivalent of volume being taken up by capacitors. Thiele et al. emphasize the role of arterial compliance in the Windkessel model,[1] but this only has a smoothing effect on the flow and little effect on the total flow because arterial compliance is so much lower than that of the veins and venules. Under flow conditions, depending on the functions of the right and left ventricles, some volume can be redistributed from the venous compliant region to other regions, but because its large compliance is so large relative to other vascular regions, the elastic recoil pressure of the venous compliant regions remains relatively constant. Furthermore, there is little volume that the heart can recruit to increase the venous elastic recoil pressure and thus venous return. Consequently, increasing pump function above normal levels only produces by itself a small increase in cardiac output. Thus, the heart functions to keep up with what is coming back, but does not increase flow much above the level of flow determined by recoil of veins and venules. This has been referred to as a "bathtub" analogy[11]; flow out of a bathtub is determined by the height of the volume in the tub (equivalent to the recoil pressure) and the drainage characteristics of the tub, and is only affected by the volume coming out of the inflow tap but not the pressure coming out of the tap. Furthermore, if there is a pump returning the draining volume to the bathtub, the pump can never increase the height of the bathtub above the starting condition. Thus, in hydraulic models, it is the initial volume that is fixed,[10] whereas in electrical models it is the pressure across the system that is fixed, but that is not the way the circulation works.

The independence of cardiac output from arterial pressure should be evident to anyone who has managed critically ill patients. For example, a septic patient has a low arterial pressure and high cardiac output, whereas a patient with major ventricular dysfunction can have a low cardiac output but increased arterial pressure. During aerobic exercise, cardiac output can increase 5-fold, but there is only a modest increase in arterial pressure. In isometric exercise, the pressure increases, but the cardiac output does not.

The consequence of a decrease in left ventricular function does not mirror an increase in function.[10] If left ventricular dysfunction is severe enough, volume accumulates in the pulmonary compartment, especially if right heart function is preserved. This shift in volume decreases the elastic recoil pressure in the systemic veins and venules and contributes to the decrease in cardiac output. Adding volume in this situation restores cardiac output but also increases pulmonary edema! Thiele et al.[1] argue that this is a limitation of Guyton's approach, because the right atrial pressure no longer predicts left ventricular filling. However, why should it, because the diastolic compliance of the left and right ventricles are not the same. However, the right atrial pressure still describes the interaction of the heart as a pump and the return function, and thus right atrial pressure is the value that should be used for assessing responses to fluids or inotropes[12]; the left heart can only pump out what the right heart gives it.

An important difference from the electrical model is that the effect of the circuit can be changed by increasing total blood volume through fluid retention or by changes in capacitance. This latter term is often confused, because in electrical models capacitance is used to define change in charge for change in voltage. The equivalence in a hydraulic system is change in volume for change in pressure. This is called compliance in pulmonary and vascular physiology. The term capacitance in vascular physiology refers to the total blood volume for total pressure and thus includes volume that is necessary to round out vessel walls but does not stretch them and is "unstressed," and the volume that stretches the vessel walls and is "stressed."[13] The reason why this is so important is that unstressed volume can be converted into stressed volume by contractions of the smooth muscles in the walls of the vessels of the compliant part of the circulation. Under resting volume-replete conditions, 10 to as much as 18 mL/kg unstressed volume can be recruited into stressed volume, and this occurs almost instantaneously because it is under neural control.[14] Recruitment of unstressed volume does not show up in electrical models, because volume is not one of the set variables.

Failure to consider the importance of the large venous reservoir has led to underappreciation of the importance of resistance draining this region.[10] Although the pressure decrease from the venous compliant region to the right heart is normally only in the range of 4 to 8 mm Hg, and only represents a small proportion of the pressure decrease from the aorta back to the heart, this pressure decrease is critical because it controls the drainage of the large venous reservoir. As will be seen, this is very important for understanding the response to phenylephrine. This resistance is in series with total arterial resistance, and is missing in the equations used by Thiele et al.[1]

Although arterial pressure is maintained relatively constant under normal conditions, as is implied in the electrical model, the stroke output of the heart is very much affected by its filling volume through Starling's law, by changes in heart rate, and by change in contractile function, so that the heart does not provide a constant flow when inflow changes and thus by itself does not provide a constant pressure or energy source to the system. Maintenance of the relatively constant normal arterial pressure occurs because of integration of the flow and arterial resistance.

Smooth muscles of small veins and venules are innervated with α-adrenergic receptors, and when these receptors are activated, vascular smooth muscles shorten and decrease the capacitance of these vessels. However, this does not usually change the slope of their pressure-volume relationship, which is the inverse of compliance. The way to think of this is that it is as if one cut out a piece of an elastic band and then put the remaining band back together, so that the change in tension for change in length is not changed but occurs at a shorter overall length. The veins draining the compliant region are innervated with α receptors, but also have β receptors. Thus, norepinephrine can constrict the capacitance vessels but at the same time does not increase the resistance draining the compliant region.[15] It has even been shown that activation of the baroreceptor reflex by hypotension constricts arterial vessels as expected but also decreases resistance in the vessels draining the compliant region of the splanchnic bed.[14] This allows more blood to drain from this region and leads to an increase in cardiac output. However, a pure α agonist such as phenylephrine constricts venous resistance vessels, which decreases the return of blood to the heart.

The cardiac output response to phenylephrine is very dependent on the starting conditions of the return function, for when left ventricular function is normal, increases in left ventricular afterload have only a small effect on cardiac output.[10] If the person is volume replete, with good reserves in unstressed volume and minimal initial tone in the veins draining the compliant region, phenylephrine can recruit unstressed volume, which will increase the venous elastic recoil pressure and, if this effect is greater than the increase in venous resistance, venous return and cardiac output will increase. This also assumes that the heart is on the ascending part of the cardiac function curve and can increase its output through the Starling mechanism. If, however, sympathetic tone is increased and a large portion of unstressed volume has already been recruited, then the effect on venous resistance will likely be dominant and venous return and cardiac output will decrease. I would predict that most critically ill patients already have a degree of sympathetic activation and thus some reduction in their recruitable unstressed volume. If the decrease in blood pressure is due to a decrease in cardiac function, and this has resulted in the right heart functioning on the flat part of the cardiac function curve, phenylephrine will have no effect, or more likely will produce a further decrease in cardiac output, as was the case in most of the studies reviewed by Thiele et al.[2] However, the arterial pressure will likely increase and provide a "tangible" comfort to the clinician!

In conclusion, the caution by Thiele et al. about being comforted by "tangible" benefits rather than true physiologic benefits needs to be heeded. It is very true for phenylephrine, but also is likely true for many other aspects of our resuscitative armamentarium. Perhaps it is also true for physiology, in which all parts of the system need to be taken into account when assessing the actions of vasoactive agents!

DISCLOSURES

Name: Sheldon Magder, MD.
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