Phenylephrine and Tangible Bias

Sheldon Magder, MD

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!

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REFERENCES

1. Thiele RH, Nemergut EC, Lynch C III. The physiologic implications of isolated alpha$_1$ adrenergic stimulation. Anesth Analg 2011;113:284–96
2. Thiele RH, Nemergut EC, Lynch C III. The clinical implications of isolated alpha$_1$ adrenergic stimulation. Anesth Analg 2011; 113:297–304
3. Goertz AW, Schmidt M, Lindner KH, Seefelder C, Georgieff M. Effect of phenylephrine bolus administration on left ventricular function during postural hypotension in anesthetized patients. J Clin Anesth 1993;5:408–13
4. Khot UN, Novaro GM, Popović ZB, Mills RM, Thomas JD, Tuzcu EM, Hammer D, Nissen SE, Francis GS. Nitroprusside in critically ill patients with left ventricular dysfunction and aortic stenosis. N Engl J Med 2003;348:1756–63
5. Goertz AW, Schmidt M, Seefelder C, Lindner KH, Georgieff M. The effect of phenylephrine bolus administration on left ventricular function during isoflurane-induced hypotension. Anesth Analg 1993;77:227–31
6. Magder S, Scharf SM. Venous return. In: Scharf SM, Pinsky MR, Magder SA, eds. Respiratory-Circulatory Interactions in Health and Disease. New York: Marcel Dekker, Inc., 2001:93–112
7. Magder S. The classical Guyton view that mean systemic pressure, right atrial pressure, and venous resistance govern venous return is/is not correct. J Appl Physiol 2006;101:1533
8. Permutt S, Caldini P. Regulation of cardiac output by the circuit: venous return. In: Boan J, Noordergraaf A, Raines J, eds. Cardiovascular System Dynamics. Cambridge, MA: MIT Press, 1978:465–79
9. Guyton AC. Determination of cardiac output by equating venous return curves with cardiac response curves. Physiol Rev 1955;35:123–9
10. Magder S, Veerassamy S, Bates JH. A further analysis of why pulmonary venous pressure rises after the onset of LV dysfunction. J Appl Physiol 2009;106:81–90
11. Magder S, De Varennes B. Clinical death and the measurement of stressed vascular volume. Crit Care Med 1998;26:1061–4
12. Magder S. Central venous pressure: a useful but not so simple measurement. Crit Care Med 2006;34:2224–7
13. Rothe C. Venous system: physiology of the capacitance vessels. In: Shepherd JT, Abboud FM, eds. Handbook of Physiology. Bethesda, MD: American Physiological Society, 1983:397–452
14. Deschamps A, Magder S. Baroreflex control of regional capacitance and blood flow distribution with or without alpha adrenergic blockade. J Appl Physiol 1992;263:H1755–63
15. Datta P, Magder S. Hemodynamic response to norepinephrine with and without inhibition of nitric oxide synthase in porcine endotoxemia. Am J Respir Crit Care Med 1999;160:1987–93

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REVIEW ARTICLE

The Physiologic Implications of Isolated Alpha$_1$ Adrenergic Stimulation

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Phenylephrine and methoxamine are direct-acting, predominantly α_1 adrenergic receptor (AR) agonists. To better understand their physiologic effects, we screened 463 articles on the basis of PubMed searches of "methoxamine" and "phenylephrine" (limited to human, randomized studies published in English), as well as citations found therein. Relevant articles, as well as those discovered in the peer-review process, were incorporated into this review. Both methoxamine and phenylephrine increase cardiac afterload via several mechanisms, including increased vascular resistance, decreased vascular compliance, and disadvantageous alterations in the pressure waveforms produced by the pulsatile heart. Although pure α_1 agonists increase arterial blood pressure, neither animal nor human studies have ever shown pure α_1-agonism to produce a favorable change in myocardial energetics because of the resultant increase in myocardial workload. Furthermore, the cost of increased blood pressure after pure α_1-agonism is almost invariably decreased cardiac output, likely due to increases in venous resistance. The venous system contains α_1 ARs, and though stimulation of α_1 ARs decreases capacitance and may transiently increase venous return, this gain may be offset by changes in afterload, venous compliance, and venous resistance. Data on the effects of α_1 stimulation in the central nervous system show conflicting changes, while experimental animal data suggest that renal blood flow is reduced by α_1-agonists, and both animal and human data suggest that gastrointestinal perfusion may be reduced by α_1 tone. (Anesth Analg 2011;113:284–96)

Phenylephrine is a direct-acting, predominantly α_1-adrenergic receptor (α_1-AR) agonist synthetically derived from epinephrine, structurally different only in its lack of an hydroxyl group at position 4 on its benzene ring.[1] It exerts mild positive ionotropic effects when administered at high concentrations.[2–4] Methoxamine is a long-acting α_1-AR agonist, synthetically derived from epinephrine but different in the number and location of side groups (including O-CH_3 groups at both the C_2 and C_5 locations of the benzyl ring, as well as a CH_3 group attached to the α carbon)[1] (Fig. 1).

Phenylephrine and methoxamine have similar effects on vascular resistance, although phenylephrine is 5 to 10 times more potent[5,6] with a 3-fold higher maximum attainable response.[5] Phenylephrine is also shorter acting; a single dose of phenylephrine generally lasts <20 minutes,[7] whereas a single dose of IV methoxamine can exert its effects for as long as 60 minutes.[7,8]

Many early studies of α_1-AR agonism were conducted with methoxamine. Methoxamine's relatively long duration of action and consequent lack of titratability, combined with the ability to variably infuse phenylephrine, have obviated its use in modern clinical practice.[9] Because their mechanisms of action are similar (predominantly α_1 agonism) and because some physiologic studies of methoxamine were never repeated with phenylephrine, this review of the physiology and experimental data of α_1-AR agonism will include data on both.

But why, some 60 years after phenylephrine was introduced into clinical practice,[10] did we choose to review the physiologic effects of these drugs?

First, practicing physicians are now squarely in the midst of a movement towards "goal-directed therapy."[11] The thought process underpinning goal-directed therapy is that, rather than using an intervention to treat an "abnormal" number, one should think critically about (a) which physiologic variables are most important (if this is known); (b) how a particular intervention affects these variables, even if they cannot be directly measured; and (c) whether manipulating these variables can change outcomes.

Favoring less important but immediately measurable variables, such as mean arterial blood pressure (MAP), over more important but less measurable variables, such as tissue oxygen delivery (DO_2), is the result of "tangible bias," our tendency to favor what we can see and understand over what we cannot. Despite the practicalities that preclude the routine measurement of regional blood flow, changes in global and regional blood flow should be anticipated any time hemodynamics are manipulated, with the goal being adequate DO_2 and nutrients to organs of interest.

Second, and equally important, is the idea that much of medical lore is based on tightly controlled animal experiments that may or may not be applicable to the intact organism. Although it may never be possible to reproduce

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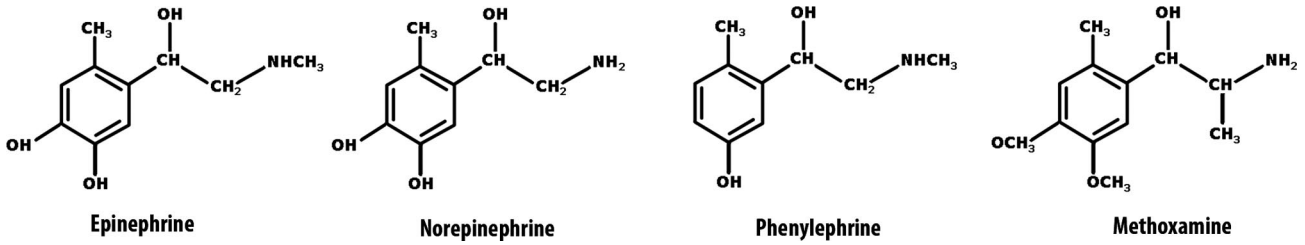

Figure 1. Chemical structure of epinephrine, norepinephrine, phenylephrine, and methoxamine.

these studies in humans in vivo, advances in mathematical modeling and computational biology (as exhibited by Magder et al.[12]) have made it possible to critically assess the validity of these long-held physiologic truths.

Thus, we critically examined the use of both methoxamine and phenylephrine. Our initial search was conducted in PubMed, using the word *methoxamine* and limiting ourselves to randomized, controlled, human trials published in English. This resulted in 28 articles, the abstracts of which were reviewed for relevance. Articles describing the hemodynamic effects of methoxamine were examined in detail. We then repeated our search using *phenylephrine* as our key word (same limits), resulting in 435 articles that were similarly reviewed, acquired, and if applicable, read. Articles brought to our attention during the review process were included as well.

Before proceeding, 3 prerequisite axioms, on which the utility of this review are based, must be established. First, this review assumes that DO_2 is critical for the survival of cells, organs, and whole organisms. Second, that for all organs and organisms, there is an optimal DO_2, which can be organ specific. Third, and perhaps most relevant, that despite a lack of data regarding the optimal DO_2 in most pathophysiologic states, anesthesiologists and intensivists will develop their own upper and lower limits of acceptability and, in general, will attempt to manipulate hemodynamics to maintain DO_2 in this range.

A COMPREHENSIVE APPROACH TO BLOOD FLOW

Rationale

When studying the effects of any vasoactive drug on the cardiovascular system, it is not sufficient to focus (as many textbooks and articles do) on an arbitrarily chosen subset of the system (e.g., systemic arteries), and in the process ignore other components (e.g., central veins, right ventricle [RV]) that also affect the system as a whole as well as the region of interest. On the other hand, isolating the individual components of the cardiovascular system, all of which interact with each other in vivo, is useful from both experimental (such experiments are easier to conduct) and educational (simplified concepts are easier to understand) standpoints.

Thus, although many of the experiments cited in this review were either conducted in isolated experimental models or focused on a subset of the cardiovascular system, their relevance depends heavily on one's ability to integrate these findings into a more global model of the cardiovascular system.

The 6-Compartment Model

This review assumes that Magder et al.'s model of the cardiovascular system closely approximates reality.[12] Specifically, Magder et al. considered the cardiovascular system to be a "6-compartment" system (right heart, pulmonary arteries, pulmonary veins, left heart, systemic arteries, systemic veins) that forms an in-series closed loop. At any point in time, all 6 compartments have a given pressure and volume. Additionally, the 4 vascular compartments can be further described by their compliance (dV/dP), whereas the 2 cardiac compartments can be further described by the rate at which they move volume (dV/dt). In accordance with the law of conservation of mass, volume that is added to (or removed from) one compartment must be removed from (or added to) an adjacent compartment.

The implications of the 6-compartment model are that blood flow through the cardiovascular system is not merely a function of just how much pressure the left heart generates and how much resistance the systemic arterioles provide, but the result of a much greater number of interacting, codependent variables. The details of these interactions will be discussed in the appropriate sections below.

Regional Versus Global Blood Flow

When the effects of any intervention on all components of the cardiovascular system are considered, it is important to distinguish global from regional changes. For example, many drug studies focus on cardiac output (CO), presumably because CO is easy to measure and changes in global flow are thought to result in similar changes in regional blood flow; however, drugs may affect global and regional blood flow inversely (e.g., increasing CO while decreasing blood flow to the kidneys). Thus, simply measuring CO changes may not give adequate insight into the utility of a particular drug, and in some instances may be misleading.

THE MATHEMATICS AND PHYSICS OF FLOW

Ohm's Law and Mathematical Notation

Textbooks commonly compare blood flow in the cardiovascular system with the flow of electrical charge (dQ/dt) across a voltage differential (E) in a single resistor (R) circuit (Ohm's law):

$$I = E/r = \mathrm{dQ/dt} \qquad (1)$$

Often, when this relationship is applied to blood flow, it is rearranged as follows (common rearrangement of Ohm's law):

$$MAP = CO \times \text{systemic vascular resistance (SVR)} \quad (2)$$

Although "mathematically correct," this equation can be misleading. Convention dictates that the dependent variables of an equation are always written on the left-hand side of an equals sign and that the independent variables are on the right. Just as the placement of a single digit has meaning when describing a multidigit number (123 does not equal 213), the location of variables in a mathematical equation is designed to convey important information. One is led to infer from Equation 2 that changes in CO affect MAP. Blood flow can most easily (and correctly) be described as follows:

$$CO = (1/SVR) \times MAP = (1/RVR_1 + 1/RVR_2 + 1/RVR_3 + \ldots + 1/RVR_n) \times MAP \quad (3)$$

(analogy of Ohm's law for global blood flow). Equation 3 introduces 2 important points – first, because the individual organs that resist blood flow exist in parallel, SVR can be related to the inverse of all individual regional vascular resistances (RVR) in accordance with Kirchoff's circuit laws ($1/R_{total} = 1/R_1 + 1/R_2 + \ldots + 1/R_n$). Second, because the body regulates blood pressure (and not CO) primarily through alterations in vascular resistance brought about by changes in sympathetic tone, MAP can remain stable over a wide variety of hemodynamic states in which CO is inversely related to vascular resistance. Thus, CO is a complex function of global efforts to regulate MAP despite multiple regional systems that alter RVR in an attempt to autoregulate.

Still, the common rearrangement of Ohm's law (Equation 2) does have practical utility in physiologic states in which CO is fixed, such as during cardiopulmonary bypass or in an autoregulated, healthy cardiovascular system. In both instances, pressure can be considered dependent on blood flow if, and only if, the pressure generator is capable of increasing pressure (with attendant increases in energy consumption) in response to increased vascular resistance.

Indeed, human studies have shown that with massive blood loss, the healthy, intact cardiovascular system will regulate MAP by manipulating afterload at the expense of CO.[13] More recent studies of the hemodynamic response to tracheal intubation have confirmed that from a whole-body perspective, preservation of MAP takes precedence over CO.[14] That said, if pressure generation is fixed or limited, blood flow will further diminish as resistance to flow is increased. It must be kept in mind that even in these idealized situations, if pressure generation were to cease, so too would the flow of blood through the cardiovascular system.

When thinking about the cardiovascular system as a whole, particularly in nonidealized situations (e.g., cardiovascular failure, loss of autoregulatory reflexes) or regional blood flow, one must appreciate that resistance to flow and pressure generated by ventricular contraction make equal contributions to the determination of both regional and global blood flow (and thus, DO_2).

Thus mathematical equations—which describe physical reality in terms that can be quantified, understood, and applied—profoundly influence our conception of reality, and are of great importance. But Ohm's law, which describes the movement of electrical current through a circuit when a constant voltage is applied, and is often used to model the human cardiovascular system, is not perfect. It does not adequately describe the movement of electrical current in cases in which the voltage differential varies with time (e.g., alternating current). When the electrical potential changes, the resulting current changes as well; how much so depends on both the resistance and the "capacitance" of the circuit.

An Introduction to Capacitance (and Compliance)

Capacitance is the ability to store potential energy. In electrical engineering, electrical capacitance ($C_{AP,elec}$) is defined as the amount of charge (Q) stored given an applied voltage potential (E):

$$C_{AP,elec} = Q/E \quad (4)$$

An electrical circuit with a high capacitance will be more resistant to rapid changes in voltage. When applied voltage is increasing, some of the current that would normally travel through the resistive elements of the circuit instead accumulates in the capacitive elements of the circuit, "smoothing out" fluctuations in current. This phenomenon is often referred to as *dampening*.

If one considers electrical capacitance, movement of current through an electrical circuit can no longer be described in simple linear terms. A differential equation is required:

$$I = dQ/dt = [E(t) - Q/C_{AP,elec}]/R \quad (5)$$

which is flow of current through an RC series circuit,[15] where E(t) is voltage as a function of time.

Similarly, the driving force of the human cardiovascular system is pressure generated by a pulsatile heart, and the vessels themselves act as capacitors. In the arterial systems, compliant vessels store mass (blood) and potential energy (pressure × volume) during systole and deliver mass (blood) and energy (pressure × volume) to the human "circuit" during diastole. The end result is that the capillary beds receive a more constant stream of blood, despite the pulsatile nature of the heart. This is referred to as the *windkessel* effect,[16] and its conceptual development is attributed to Otto Frank.[17]

The major systemic arterial capacitance vessels include the aorta and large arteries, which exist in parallel with the resistive elements of the vasculature, and because the upper and lower body contain capacitance vessels of different lengths, the systemic vascular system is most appropriately modeled as a 2-capacitor circuit.[18] A major difference between the cardiovascular system and an analogous electrical circuit is that the cardiovascular system stores mass (volume), not charge.

Volume exists in 2 states: hemodynamically inactive "unstressed" volume (defined as the amount of blood present in the venous system where venous transmural pressure is 0 [approximately 70% of total venous blood volume]), and hemodynamically active "stressed" volume (defined as the difference between total venous blood

volume and unstressed volume).[19] From the standpoint of measuring flow as a function of changes in pressure, volume, compliance, and resistance, it is only the stressed volume that matters. Importantly, hemodynamic changes (e.g., vasoconstriction) can convert "unstressed" volume to "stressed" volume as a compensatory means,[20] without necessarily changing vascular compliance.[19] There is no electrical equivalent for "unstressed volume."

Thus, it is useful to think of the vasculature not only in terms of the amount of volume stored at a given pressure (defined as vascular capacitance, Equation 6), but also in terms of vascular *compliance*, defined as a change in volume that results from a change in pressure (Equation 7).[19] Vascular compliance is inversely related to vessel stiffness (κ). Vascular capacitance is defined as

$$C_{AP,vasc} = V/P \quad (6)$$

and vascular compliance as

$$C_{OM,vasc} = \Delta V/\Delta P = 1/\kappa. \quad (7)$$

Note that while convention dictates that the ability to store electrical energy in the form of charge is referred to as *electrical capacitance*, the ability to store energy in the form of pressure is more appropriately described by vascular compliance (because it appropriately neglects the "unstressed" volume that is energetically inactive), and for the purposes of this analogy, electrical capacitance (Q/E) and vascular compliance ($\Delta V/\Delta P$) can be considered interchangeable, although they will be abbreviated as $C_{AP,elec}$ and $C_{OM,vasc}$ (or $1/\kappa$), respectively.

As with the electrical circuit driven by an oscillating voltage potential, blood flow through a compliant vessel is not simply a function of "resistance," but must also consider arterial compliance and the volume of blood contained in the vessel at that moment:

$$Q = dV/dt = P/R + dP/dt \times (C_{OM,vasc}) = P/R + dP/dt \times (1/\kappa)$$

Equation 8 describes blood flow through a compliant vessel, or what is known as the "Two Element Windkessel Model." Models incorporating up to 4 elements have been developed, and increasingly approximate experimental observations.[21,22]

Therefore, although hemodynamic data can be used to calculate systemic vascular "resistance," this value is a combination of resistance to blood flow when a constant driving force is applied, the instantaneous directional change in pressure (dP(t)/dt), and compliance, all of which affect blood flow—their relative contribution changes depending on the hemodynamic state. To truly appreciate the oscillatory component of afterload, one must decompose both the pressure and flow waveforms into their harmonic components, the end result of which is the bipartite concept of vascular impedance (abbreviated *Z*, comprising modulus and phase), the details of which are beyond the scope of this review but are thoroughly detailed elsewhere.[23]

Arterial compliance may also affect myocardial oxygen consumption (mVO_2). Kelly et al.[24] studied the effects of compliance changes on ventricular efficiency in adult dogs, by altering the compliance of the abdominal aorta with a rigid plastic graft. The plastic conduit reduced arterial compliance by 60%–80%, resulting in an 11.9% increase in MAP despite a 10.5% decrease in CO (calculated SVR increased by 20%). Despite the roughly equal oppositional changes in pressure and volume, implantation of the rigid graft resulted in a 32% increase in mVO_2 and a 32% decrease in ventricular efficiency, reflecting the relatively substantial contribution of pressure work (energy intensive, in comparison with volume work) in the determination of myocardial oxygen needs. Interestingly, the increase in myocardial consumption was directly proportional to the increase in pressure volume area (PVA; see PUMP WORK AND VENTRICULAR EFFICIENCY section, below); however, because the authors did not increase vascular resistance independently of compliance, it is impossible to know for certain whether an isolated decrease in compliance also worsens ventricular efficiency.

The venous systems, by contrast, are much more compliant than are the arterial systems, and, by comparison, store more volume (70% of total blood[25]) and less potential energy. Thus, although arterial compliance primarily affects the arterial waveform and afterload, venous compliance impacts the cardiovascular system through several different mechanisms, all of which are based on an understanding of the venous function curve and the concept of mean circulatory filling pressure (MCFP).

Venous Function Curve

The venous function curve, as originally described by Guyton,[26] describes the effect of changes in right atrial pressure (RAP) on venous return: as RAP is increased, venous return (and CO) decreases, and ultimately becomes zero as RAP approaches MCFP. Similarly, as RAP is decreased, venous return increases, reaching a maximum at the point at which veins collapse (atmospheric pressure, or higher in the setting of positive end-expiratory pressure).

Guyton's venous function curves can also be understood working backwards, i.e., starting from the position of no CO.[19] When CO is zero, blood pressure in the pulmonary and systemic arterial and venous systems will be equal; this is referred to as the MCFP, and is a function of total blood volume as well as arterial and venous compliance in both the pulmonary and systemic vasculatures. As the left ventricle (LV) and right ventrical (RV) begin to pump blood, arterial pressures will increase above MCFP. Venous pressures will decrease below MCFP, thereby establishing a pressure gradient (required for blood flow) across the pulmonary and systemic vasculatures, and shifting volume from the venous compartments to the arterial compartments. As CO increases further, arterial pressures will necessarily continue to increase, venous pressures will continue to decrease, and increasing volume will be shifted towards the arterial compartments.

For a given blood volume and vascular compliance, the cardiovascular system can exist at any state that lies on its venous function curve. Traditional teaching espouses that this state depends on where the venous function curve intersects the CO curve (because, at steady state, total venous blood return must equal CO). The CO and venous

function curves are often plotted together to make this calculation, which can be misleading because although RAP is closely related to right ventricular preload, the ability of RAP to reflect LV preload is dependent on the physiologic state of the pulmonary vascular tree as well as on that of the left ventricle.

This added complexity complicates Guyton's classic teaching and suggests that Guyton's venous function curves, which were derived in experimental animal models, may not be directly applicable in vivo.[27–29] Regardless, Guyton's major premise, that venous return is just as important as cardiac outflow in determining steady-state blood flow, still holds true, and has major implications, as noted below.

Despite the controversy surrounding the shape of the venous function curve in vivo, it is generally thought that venous compliance impacts CO through 3 mechanisms. First, because venous pressures decrease with increasing CO but cannot decrease below the point of venous collapse, the maximum attainable CO is impacted by both blood volume and venous compliance (or, as was more precisely described by Levy in 1979, the ratio of venous to arterial compliance[30]). Second, steady-state CO is at least partially dependent on the configuration of the venous function curve, which is a function of venous compliance. Third, by redistributing blood volume towards (or away from) the central vessels, atria, and ventricles,[31] changes in venous resistance and compliance can profoundly affect ventricular end diastolic volume, and thus CO.[32]

Relative Importance of Arterial and Venous Vascular Resistance

Because the majority of SVR is provided by the arterioles, it may seem counterintuitive that venous resistance and compliance could significantly impact CO. Indeed, 51 years after Guyton published his venous function data, the utility of his models was still being debated in the literature.[33,34]

The debate about whether Guyton's models are applicable in vivo is a misunderstanding of his experiments and his conclusions. Guyton's venous function curves were developed by cannulating the right atrium and aorta,[26] bypassing both ventricles and the lungs. A mechanical pump (connected in series with a piece of collapsible tubing, connected proximally [i.e., a "Starling resistor"]) was placed in between.[33,35] As the height of the Starling "resistor" was changed, inflow to the pump was variably throttled, resulting in changes in both RAP and venous return. Technically, the independent variable in this arrangement was flow[33,35] (determined by the Starling resistor), not RAP (although if one accepts that blood moves down a pressure gradient, the origin of the pressure gradient is not relevant). Maximal output was limited by the point at which the tubing collapsed (0 mm Hg). This arrangement is not necessarily what happens in live animals with a closed chest and interacting pulmonary and systemic circulations, pumps that depend on preload, varying thoracic pressures, and central venous systems that may, in some instances, remain patent even at subatmospheric pressures. Studies of closed-chest humans after cardiac surgery have produced mixed results. Some authors have suggested that Guyton's relationship holds,[27] and others have failed to elucidate a relationship between venous return and P_{RA}.[29] Thus, Guyton's initial experiments, which established that decreased resistance to venous return (and the resultant increase in venous pressure gradients) lead to increased venous return in an experimental system, were unable to attribute these changes in venous return to changes in RAP.

To better understand the impact of changes in venous resistance on venous return and CO, Guyton compared selective increases in either arterial or venous resistance in anesthetized dogs (right-heart bypass preparation).[36] Vascular reflexes were abolished using spinal anesthesia. Arterial resistance was then increased by injecting glass beads into the aorta, and venous resistance was increased by tightening inflatable cuffs implanted around the vena cava.

Interestingly, doubling SVR via the injection of glass beads led to a 15% decrease in CO and a 75% increase in blood pressure, whereas doubling SVR via constriction of the vena cava reduced CO by 65%, presumably by sequestering blood in the venous system, and thus depriving the ventricles of the preload needed to maintain CO (postulated, but not proven, by Guyton in this article[36]). Indeed, no amount of isolated arterial resistance (even a 500% increase in SVR) could decrease CO to the extent achieved by a relatively modest increase in venous resistance (50% increase in SVR via constriction of vena cava).

Clearly, the canine left ventricles in this experiment were better able to maintain stable CO despite increased arterial resistance, in comparison with increased venous resistance. This was likely due to differences in vascular distensibility. Arteries, which are relatively nondistensible, are unable to remove significant volume from the circulation despite increased resistance to flow. Increased arterial resistance does not markedly decrease cardiac filling unless the heart cannot maintain constant CO despite increased afterload. By contrast, veins, which are highly distensible (compliant) and store approximately 70% of total blood volume, can almost immediately sequester relatively large amounts of blood despite increased resistance to flow, essentially robbing both the left and right ventricles of preload.

Thus, in 1958, Guyton's experimental data began to provide proof that the all-encompassing concept of "systemic vascular resistance" and tacit assumption that SVR is due to arterial tone may not be physiologically relevant, because the location of vascular resistance is critical and is not accounted for by simply dividing pressure gradients by CO. This idea was further refined by separating the regulation of venous flow into changes in compliance and resistance, which can occur independently of one another.[19]

Pressure Wave Reflections

Further complicating hemodynamic predictions is the 3-dimensional shape of the cardiovascular system. Whereas electrical circuits are made of wire that rarely vary in size, shape, or composition, the "wires" of the human cardiovascular system vary greatly, both in terms of their stiffness and shape as well as their branch points.

As a pressure wave travels down the vascular tree, it meets additional resistance at places where the vascular tree branches or where vascular impedance (a combination of resistance and compliance) changes quickly.[37] At these branch points and changes in impedance, part of the pressure

wave is reflected back towards the heart (much as ultrasound waves emitted by an echocardiography probe are partially reflected by tissue interfaces), thus reducing the driving force for forward blood flow. Normally, these pressure waves reach the left ventricle during diastole, where they can either contribute to coronary perfusion[38] or be absorbed by the closed aortic valve. In cases in which vascular compliance is significantly reduced (e.g., with atherosclerosis or aging), these reflected pressure waves travel more quickly, and can arrive back at the left ventricle before aortic valve closure, decreasing the speed of myocyte shortening.[39]

The relative contributions of resistance, compliance, and pressure waves to ventricular afterload are difficult to tease apart, because most interventions (e.g., vasoconstrictors) affect all 3 variables simultaneously.[37] In addition to increasing arteriolar resistance, vasoconstrictors (including phenylephrine[6]) appear to augment these arterial tree reflections by decreasing compliance and accelerating pressure wave conduction.[40]

SUPPLY AND DEMAND—THE ECONOMICS OF CARDIAC PERFORMANCE

Oxygen delivery (DO_2) is preeminently important in the context of oxygen consumption (VO_2). Thus, when considering the hemodynamic effects of drugs on the heart, one must have an appreciation for both coronary artery perfusion (supply) and mVO_2 (demand).

Supply (Coronary Artery Perfusion)

Heyndrickx et al. studied the effects of methoxamine on coronary blood flow in healthy, conscious dogs, with both paced and spontaneously beating hearts. In the paced hearts, methoxamine increased coronary blood flow, whereas in the spontaneously beating hearts, coronary blood flow decreased 8% (despite increasing MAP by 55%, and decreasing heart rate by 13 beats per minute [bpm]).[41] Woodman and Vatner[42] gave phenylephrine (0.5 and 1 μg/kg/min) to unanesthetized dogs autonomically blocked with hexamethonium, propranolol, and atropine and found that phenylephrine increased MAP but had no effect on coronary blood flow. Crystal et al.[43] administered phenylephrine (2.8 μg/kg/min) to anesthetized dogs and found that although myocardial blood flow increased by 60%, mVO_2 increased by 61%. Neither arterial–coronary sinus oxygen difference, coronary sinus Po_2, or coronary sinus saturation changed significantly.

Miller et al. studied the effects of phenylephrine on coronary blood flow in humans, by administering nitroglycerin to 17 paced patients undergoing cardiac diagnostic catheterization (MAP decreased by an average of 10.5 mm Hg), and then randomizing them to phenylephrine (50 to 90 μg/min) versus no intervention. At 10 minutes postnitroglycerin, coronary sinus blood flow was significantly higher in the phenylephrine group.[44] Indeed, studies of α_1 receptor density in humans have confirmed that the coronary arteries contain α_1 receptors, although the amount (2.1 fmol/mg protein) is significantly less than that found in the other, similarly sized arteries, such as the mammaries (6.0 fmol/mg protein).[45]

Loeb et al.[46] studied the effects of methoxamine (2 mg/min) in 20 patients with stable, ischemic heart disease (mean MAP 90 mm Hg before intervention), finding that it increased coronary sinus flow by 82% but also increased mVO_2 by 77%. The arterial–coronary O_2 saturation difference was unaffected (64% in both instances), however. Fifteen percent of patients receiving methoxamine displayed ST segment changes.

Antonopoulos et al. administered phenylephrine (80 μg/min) to 41 hemodynamically stable patients with documented coronary artery disease, increasing MAP by 30% above baseline. Sixty seconds after achieving an increase in blood pressure, 2 mCurie (mCi) of thallium (Tl) were injected and Tl scintigraphy was performed 2 and 240 minutes after Tl injection. Scintigraphy after phenylephrine infusion revealed 152 defects (average 14% of evaluated segments), and the size of the defect was directly related to the number of diseased vessels. The authors concluded that blood pressure increase accompanying phenylephrine produced a significant impairment of myocardial perfusion.[47] Unfortunately, the authors did not include data on myocardial perfusion before administration of phenylephrine.

Taken together, these studies suggest that although increased pressure can maintain global perfusion, depending on how achieved, it may still lead to a maldistribution of regional myocardial blood flow.

Demand (Afterload)

Afterload (σ) is a measure of the forces against which the heart must work to generate a given CO. In its purest form, it is defined as the forces opposed to LV fiber shortening (i.e., LV wall stress).[48] SVR is considered by most practitioners as equivalent to afterload.[48] However, as noted above, SVR is an oversimplified quantification of hemodynamics.

Unfortunately, true afterload cannot be readily measured except in the experimental setting. It can be best approximated by calculating circumferential wall stress (S), in a variation of Laplace's law known as *Lame's equation*.[37] Although more difficult to calculate than is SVR, it gives a more accurate indication of cardiac energy expenditure, and is more specifically proportional to mVO_2.[49]

$$S = Pr/h \qquad (8)$$

where S = wall stress, P = pressure, r = radius, and h = thickness. An important implication of Lame's equation is that afterload is not simply a function of resistance, compliance, and wave reflections, but is also dependent on the geometry of the left ventricle itself. During systole the ventricular wall thickens as its radius contracts, which reduces LV wall stress. In the latter half of systole, afterload is reduced simply because LV radius is smaller and wall thickness is greater. All other things being equal, a heart operating with more shortened myocytes (e.g., as may occur after β adrenergic stimulation) will work against less "afterload," because it will spend proportionately more time in a favorable (smaller radius) geometrical configuration.

Lang et al. studied the effects of methoxamine, nitroprusside, norepinephrine, and dobutamine on 8 anesthetized, intubated, and catheterized (left and right heart) but otherwise healthy dogs.[48] Using Grossman's previously validated method[49] to calculate afterload, Lang et al. found that SVR is an almost 2-fold underestimate of LV wall stress after administration of methoxamine (SVR increased 48%, whereas LV wall stress increased 86%). Norepinephrine led

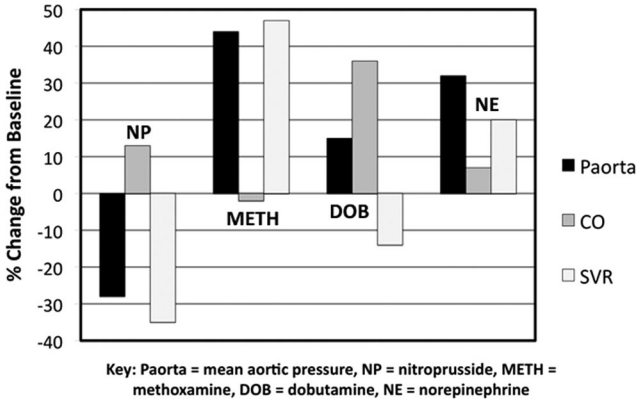

Figure 2. Effect of pharmacologic agents on blood pressure, cardiac output, and SVR. Effect of nitroprusside, methoxamine (pure α-agonist), dobutamine, and norepinephrine on aortic pressure, cardiac output, and systemic vascular resistance in healthy dogs (redrawn from Lang et al.,[48] with written permission from Wolters Kluwer Health). MCFP = mean circulatory filling pressure; LVEDV = left-ventricular end-diastolic volume.

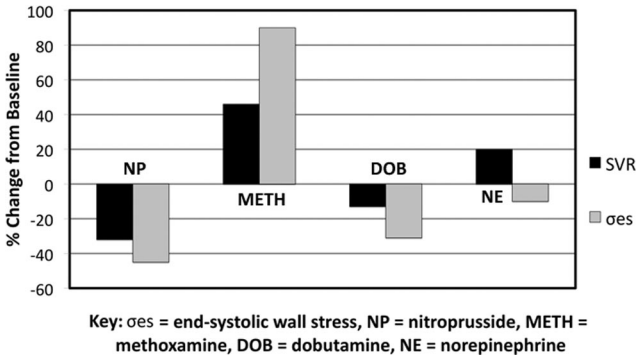

Figure 3. Effect of pharmacologic agents on SVR and end-systolic wall stress. Comparative effects of nitroprusside, methoxamine (pure α-agonist), dobutamine, and norepinephrine on systemic vascular resistance (SVR) and afterload (defined as end-systolic wall stress, σ_{es}) in healthy dogs. Note that for norepinephrine, SVR is positive, whereas σ_{es} is negative, thus invalidating SVR as an indicator of afterload (redrawn from Lang et al.,[48] with written permission from Wolters Kluwer Health). CO = cardiac output.

to a 21% increase in calculated SVR, but measured LV wall stress actually decreased by 9% because of increased contractility and a subsequent decrease in ventricular size. Thus, in some instances, SVR is not simply off by a percentage, it changes in the opposite direction of wall stress[48] (Figs. 2 to 4).

Guyton et al.'s experiments on selective vascular resistance further support this view, because changes in SVR bore almost no relationship to changes in either CO or afterload. Indeed, isolated increases in arterial resistance led to significant increases in aortic blood pressures, whereas equivalent increases in venous resistance led to almost no change in aortic blood pressure.[36]

PUMP WORK AND VENTRICULAR EFFICIENCY

Pump (Mechanical) Work

Afterload, which measures force, is related to but distinct from work, the application of force over distance. Pumps work by applying pressure to a displaced volume, and

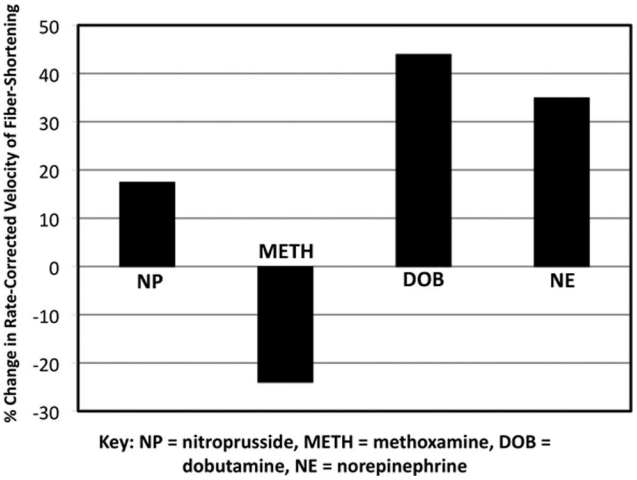

Figure 4. Effect of pharmacologic agents on left ventricular function. Effects of nitroprusside, methoxamine (pure α-agonist), dobutamine, and norepinephrine on left-ventricular performance (as measured by velocity of left-ventricular fiber shortening, Vcf_c) in healthy dogs (redrawn from Lang et al.,[48] with written permission from Wolters Kluwer Health). SVR = systemic vascular resistance.

produce both pressure work (increasing pressure) and volume work (movement of volume), both of which require the expenditure of energy. Mathematically, the amount of mechanical work done by a pump is represented by the area inside the curve of a pressure–volume (PV) loop:

$$W = -\int_{V_1}^{V_2} P dv \qquad (9)$$

Note that although pressure work and volume work can be thought of separately, neither can occur in the absence of the other. Increased pressure without moving volume does not result in work, nor does moving volume if pressure is not accordingly increased.

In situations in which CO (volume pumped) is desired, pressure work is inefficient because increased ventricular pressures necessitate the formation and release of additional myosin–actin cross-bridges (which consumes adenosine triphosphate), but does not increase flow. The shape of the PV loop can provide a visual estimate of volume-based ventricular efficiency. Multiple studies in humans have shown that phenylephrine reduces CO and increases measured vascular resistance,[50–52] which heightens the resultant PV loop, and usually decreases stroke volume (Fig. 5).[53,54]

Internal Work

Unlike an inanimate, mechanical pump (e.g., internal combustion engine) that requires no energy when not functioning, the heart requires energy to maintain its cellular integrity even when not contracting.

In addition, the heart requires energy expenditure to generate pressure even when no volume is moved. This is referred to as *internal work* (also termed *potential energy*) and can be attributed to electrical activation and excitation–contraction coupling (calcium cycling).[55]

Suga et al. noted that differing combinations of pressure and volume work (which produce an identical amount of

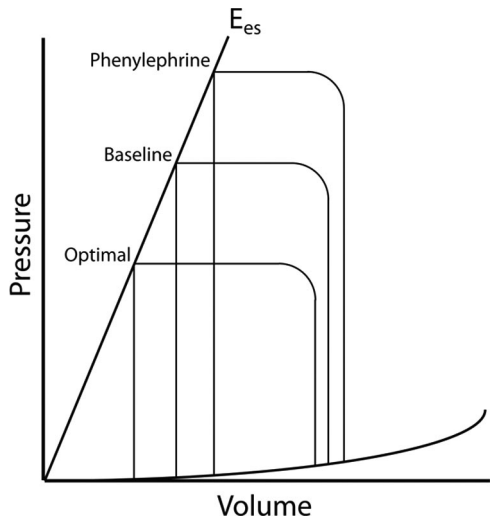

Figure 5. Effect of phenylephrine on the pressure–volume loop in the setting of human heart failure (adapted from Asanoi et al.,[53] with written permission from Wolters Kluwer Health).

mechanical work) require different amounts of oxygen consumption,[55,56] and that these differences could be attributed to increases in internal work required to function at different physiologic states (Fig. 6A). Unlike the PV loop area, total pressure–volume area (PVA, Fig. 6, B–C) reliably estimates myocardial VO_2 in an isolated canine heart model, as was shown by Suga,[57–59] Khalafbeigui,[60] and Burkhoff[61] in a series of experiments conducted over a period of 10 years.

Ventricular Efficiency

The term *ventricular efficiency* has several definitions, but is usually thought of as CO per milliliter of oxygen consumed. Note that this definition assumes that the quantity of blood flow is more important than the pressure required to deliver it. From this volume-based ventricular efficiency standpoint, increased pressure work and internal work are wasteful and should be minimized.

Phenylephrine decreases volume-based ventricular efficiency by shifting myocardial mechanical work from volume to pressure work, and presumably by increasing internal work (although PVA has not been specifically studied in humans, this can be surmised by analyzing the resulting PV loops, Fig. 5). A study comparing phenylephrine with epinephrine, norepinephrine, dopamine, dobutamine, and isoproterenol in piglets under general anesthesia suggested that of these 6 vasoactive drugs, phenylephrine was the only one that did not increase the CO/PVA ratio.[62]

In instances in which perfusion pressure is deemed more important than global blood flow (e.g., optimizing cerebral perfusion pressure), volume work is wasteful, because it does not necessarily lead to increased blood pressure but still requires additional mechanical work (and expenditure of energy). Thus, from a practical standpoint, the "efficiency" of the heart depends not only on work done per energy consumed, but also on what type of work is needed most (volume or pressure).

EFFECT OF ALPHA-ADRENERGIC AGONISTS ON INDIVIDUAL ORGAN SYSTEMS

Cardiovascular System

Left heart and CO. Smith et al.[63] randomized 60 carotid endarterectomy patients to anesthesia (MAC 1.04) with no ionotropic drugs versus deeper anesthesia (MAC 1.43) with administration of phenylephrine to maintain systolic blood pressure within 20% of baseline. Intergroup differences in blood pressure were insignificant; however, the phenylephrine group was burdened with a 40% increase in LV end-systolic wall stress as estimated by transesophageal

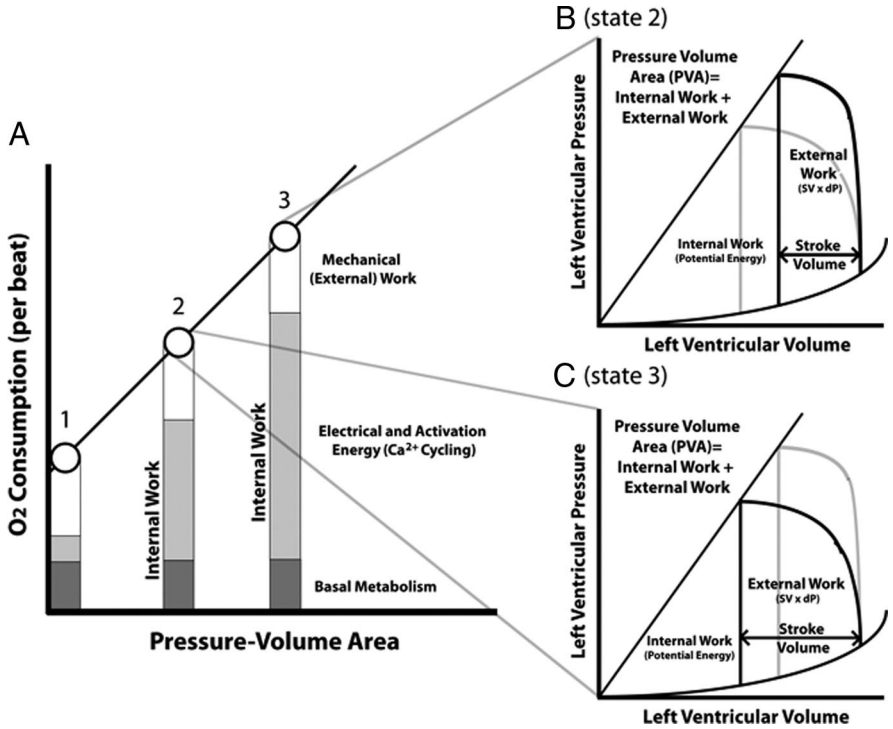

Figure 6. A, Relationship between myocardial oxygen consumption and pressure–volume area [PVA, defined as internal work + external work] at a constant level of external work. B, Myocardial energetics at state 2 [high-pressure work, low-volume work]. C, Myocardial energetics at state 3 [high-volume work, low-pressure work]. All figures derived from experiments using the isolated canine heart model.

echocardiography, a 160% increase in the incidence of segmental wall motion or wall thickening abnormalities, and a 32% reduction in the rate-corrected velocity of circumferential fiber shortening.

Goertz et al.[64,65] compared phenylephrine to norepinephrine in both volunteers and cardiac surgery patients, both under general anesthesia. In 16 volunteers (2 μg/kg of phenylephrine vs. 0.1 μg/kg of norepinephrine) and 38 cardiac surgery patients (2 μg/kg of phenylephrine vs. 0.05 μg/kg of norepinephrine), both drugs produced identical changes in MAP, but phenylephrine produced significantly higher wall stress (estimated from transesophageal echocardiographic measurements) and significantly lower fractional area change (and presumably, CO) in comparison with norepinephrine.

Sharrock et al.[50] compared phenylephrine (2 to 20 μg/min) with epinephrine (1 to 5 μg/min) in 30 patients undergoing epidural anesthesia and found that despite no difference in MAP, phenylephrine led to slower heart rate and CO.[52] Brooker et al. conducted a similar study in 13 patients undergoing spinal anesthesia and found that phenylephrine significantly reduced CO, in comparison with epinephrine.[51] Langsesaeter et al. also studied the effects of phenylephrine (0.25 μg/kg/min) in patients undergoing spinal anesthesia, comparing it with placebo in 80 women undergoing cesarean delivery. While phenylephrine clearly increased systolic blood pressure, it also led to significant reductions in CO in comparison with that in controls. A more recent comparison of phenylephrine infusion rates in the setting of spinal anesthesia for elective cesarean delivery found that the maximal decrease in CO was linearly related to the dose.[66]

Systemic venous return. Multiple animal studies have shown that α_1-agonists are venoconstrictors, and thus capable of increasing MCFP.[2,67–69] Appleton et al., for instance, found that 8 to 20 μg/kg/min of phenylephrine increased MCFP by 49% in lightly sedated dogs.[2]

Although an isolated increase in venous tone may transiently increase CO, whether or not a pharmacologically mediated increase in venous tone leads to increased venous return in the intact organism has been debated.[70] Unlike the increased skeletal muscle tone that accompanies exercise, or the increase in stressed volume that occurs after fluid administration, all of the known drugs that increase venous tone have the potential to cause accompanying increases in arterial and venous resistance, potentially negating any improvements in venous return.[71]

In an illuminating review, Gelman and Mushlin pointed out that 25% of total body blood volume is present in the splanchnic organs, making them an important hemodynamic reservoir. Furthermore, they suggested that α_1-agonists have a dose-dependent effect on venous return; the initial response being an increase in venous return as the splanchnic vasculature is "unloaded," followed by a decrease in venous return at higher doses as the effects of vasoconstriction and venoconstriction (decreased organ outflow) predominate.[72]

The idea that the splanchnic circulation is an important reservoir for venous blood is strongly supported by Flamm et al.'s study of blood volume distribution in exercising humans. Flamm's group exercised 14 healthy volunteers on stationary bikes, increasing workloads from rest (VO_2 averaged 5.8 mL/kg/min) to VO_{2max} (average 39 mL/kg/min). CO increased by 170% at maximal values, but organ-specific blood volumes (measured with technetium 99-m scanning) decreased by 46%, 24%, and 18% in the spleen, kidneys, and liver, respectively. By contrast, organ-specific blood volumes increased by 50% and 24%, respectively, in the lungs and heart.[32]

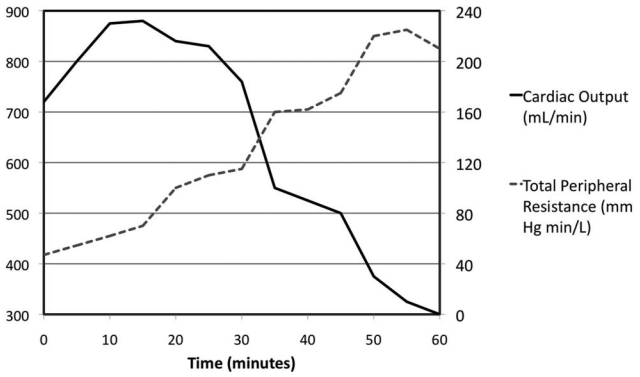

Figure 7. Effect of escalating doses of methoxamine on cardiac output and peripheral resistance. Escalating dose response of methoxamine (long-acting pure α agonist) on the hemodynamic state of dogs after administration of spinal anesthesia (dose started at 0.3 mg/kg/h, increased by 0.3 mg/kg/h every 15 minutes; redrawn from Zandberg et al.,[73] with written permission from Wolters Kluwer Health).

Particularly appealing about the splanchnic venous reservoir concept is the fact that the splanchnic vasculature exists in parallel ($1/R_{Total} = 1/R_1 + 1/R_2 + \ldots + 1/R_n$) with the remainder of the systemic circulation, thus attenuating the increase in venous resistance that would otherwise accompany venoconstriction, while at the same time allowing the body to mobilize a significant amount of volume.[19]

Thus, it appears that α_1-agonists' effects on the venous circulation have the ability to both increase (by reducing venous compliance, thus converting unstressed volume to stressed volume and increasing preload) and decrease (primarily through increases in venous resistance) CO. The end result is likely related to dose of the drug and the sensitivity of the individual organism and tissues. This idea is supported by Zandberg et al.'s dose-response study of methoxamine in dogs who had undergone spinal anesthesia. Initially, methoxamine increased both CO (maximally at 0.6 mg/kg/h of methoxamine) and blood pressure, although at increasing doses, CO began to decrease[73] (Fig. 7). Interestingly, calculated SVR was increased even at low doses (0.3 to 0.6 mg/kg/h), suggesting that the increased CO was due to increases in stressed volume and preload.

A limited number of human studies also support the idea that α_1-agonists reduce venous compliance and potentially increase venous return. In 1975, Marino et al. compared the effects of phenylephrine, isoproteronol, dopamine, and phentolamine on perfusion pressures and reservoir volumes in 73 patients undergoing cardiopulmonary bypass. Marino et al.'s experiments showed significant increases in cardiopulmonary bypass reservoir volumes after administration of both phenylephrine (0.3 mg) and low- (0.2 mg) and high- (4 mg) dose dopamine (by

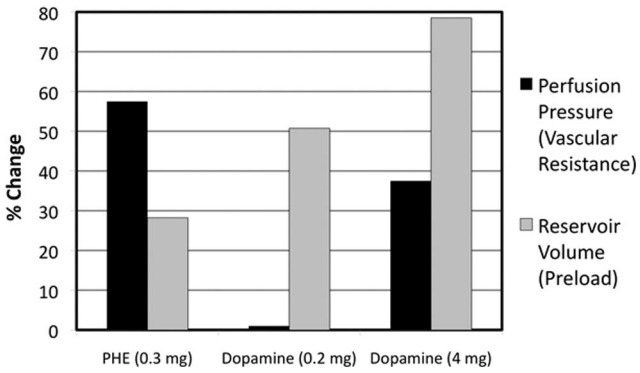

Figure 8. Effects of phenylephrine and dopamine on vascular resistance and preload as measured by changes in perfusion pressure and venous reservoir volume on the basis of measurements in patients on cardiopulmonary bypass (adapted from Marino et al.,[74] with written permission from Wolters Kluwer Health).

247, 444, and 687 mL, respectively), suggesting that both drugs decrease venous compliance through enhanced tone. Perfusion pressures changed by 23, 0.13, and 15 mm Hg, respectively, suggesting that phenylephrine and high-dose dopamine increased vascular resistance (and thus, afterload), whereas low-dose dopamine had no effect on vascular resistance, despite its ability to increase venous return[74] (Fig. 8).

Right heart and pulmonary circulation. Because systemic compliance is approximately 7 times that of the pulmonary circulation,[67,69] the pulmonary vascular system cannot store as much latent "preload" as does its systemic counterpart. That said, because the left heart relies on the right heart for preload, and the right heart traditionally faces significantly less afterload than does the left, changes in pulmonary vascular resistance can profoundly impact the cardiovascular system as a whole.

Studies of α_1 receptor density in humans have shown that the pulmonary arteries contain a higher density of α_1 receptors than does any nonsplanchnic organ.[45] Tuman et al. examined the effects of phenylephrine on right ventricular function in patients undergoing coronary artery surgery, and found that postinduction phenylephrine (titrated to increase systolic blood pressure to 20% above baseline) significantly increased right ventricular end-diastolic volume index (RVEDVi) (from 86.3 to 97.5 mL/m^2, $P = 0.0001$)[75] without significantly impacting cardiac index. Pulmonary vascular resistance, however, increased from 62.0 to 157.2 dyne · s · cm^{-5}, suggesting that the increase in RVEDVi was due to an increase in pulmonary vascular resistance, and not venous return.

Brain

It is generally thought that the cerebral vasculature lacks significant α_1 receptors, mostly on the basis of animal experiments (such as Harik et al.'s data from rat and pig models[76]), although this assertion is refuted by other data from bovine,[77] rat,[78] and gerbil[79] models, as well as some human data.[80]

Nevertheless, phenylephrine has been used to increase cerebral perfusion pressure. Although Doppler studies have been used to suggest that cerebral autoregulation is intact during general anesthesia,[81] they have also been used to show that phenylephrine increases blood flow velocity in the intracranial vessels of animals with experimental neurologic injuries (and presumably a disrupted cerebral autoregulatory curve).[82] However, increased velocity does not necessarily imply increased flow, especially if achieved through the actions of a vasoconstrictive drug.

Studies of phenylephrine on cerebral blood flow (CBF), as opposed to velocity, are rare. Kitaguchi et al. studied the effects of methoxamine on 10 patients with ischemic cerebrovascular disease undergoing extraintracranial artery bypass and, using the Kety–Schmidt inert gas saturation technique, found no relationship between CBF and methoxamine-induced increases in MAP.[83] Joseph et al. studied the effects of phenylephrine on 5 vasospastic subarachnoid hemorrhage patients and found that mean CBF in the right frontal cortex increased by 75% in the vasospastic cortical regions, but did not report CBF in the nonvasospastic cortical regions.[84]

Kidneys and Other Organs

Studies of α_1 receptor density in humans have shown that the renal arteries contain a relatively high density of α_1 receptors (24 fmol/mg protein), in comparison with other, similarly sized vessels, such as the mesenteric arteries (13 fmol/mg protein).[45] Human physiologic studies are largely absent; however, Grangsjo and Persson[85] studied the administration of vasoactive drugs on canine renal blood flow. Three normotensive dogs under general anesthesia received methoxamine (doses ranged from 0.17 to 0.6 mg/kg), which immediately resulted in significant reductions in urine output (in 1 animal, measured renal blood flow decreased from 110 to 10 mL/min) and total cessation of urine output within minutes. Three hypotensive dogs (bled through a femoral artery catheter to blood pressure [systolic or diastolic not distinguished] <50 mm Hg) also received methoxamine (0.3 to 1 mg/kg), which similarly reduced renal blood flow by 70%–80%, despite significant increases in blood pressure and renal perfusion pressure (Fig. 9). Norepinephrine, by contrast, increased medullary blood flow and resulted in an increase in urine output when administered as a continuous infusion (0.03 to 0.6 μg/kg/min) in Grangsjo and Persson's experiments.[85] At least 1 case of overt renal failure induced by phenylephrine administration in humans has been reported.[86]

Hoffbrand et al. administered vasopressors to unanesthetized rhesus monkeys, and found that although norepinephrine (0.5 to 3 μg/kg/min) redistributed CO towards the heart and skeletal muscles, methoxamine increased vascular resistance uniformly and reduced CO at both low (20 to 100 μg/kg/min) and high (150 to 500 μg/kg/min) doses (by 20% and 43%, respectively). Both doses of methoxamine significantly reduced blood flow to the kidneys, spleen, pancreas, and lungs, and high-dose methoxamine significantly reduced blood flow to the brain (regional resistance increased by 54%), heart (regional resistance increased 79%), gastrointestinal tract, and skeletal muscles, and of all the organs measured, spared only the adrenals[87] (Fig. 10).

Heyndrickx et al. found that when escalating methoxamine doses from 5 to 50 μg/kg/min in healthy, conscious dogs, MAP values increased to 25, 35, and 55% above baseline, but CO decreased by 9% at lower doses and by as

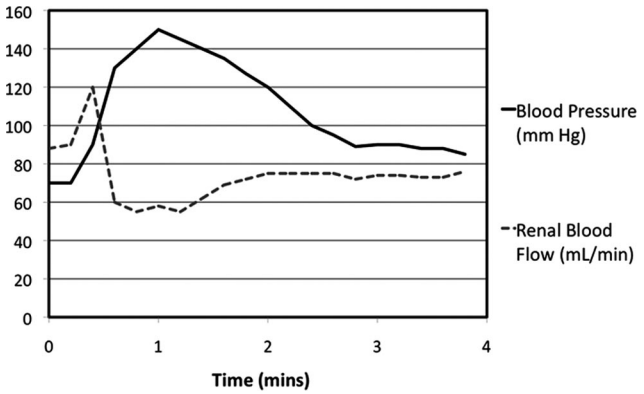

Figure 9. Effects of methoxamine (0.1 mg/kg IV) on blood pressure (solid line) and renal blood flow (dashed line) in mongrel dogs under general anesthesia (redrawn from Grangsjo and Persson,[85] with written permission from publisher John Wiley and Sons).

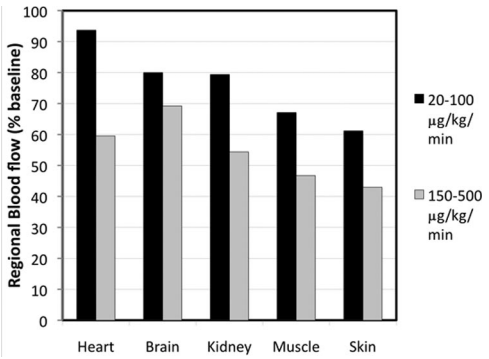

Figure 10. Effects of methoxamine on regional blood flow in unanesthetized Rhesus monkeys at both low and high doses (adapted from Hoffbrand and Forsyth,[87] with written permission from the publisher, The American Society for Pharmacology and Experimental Therapeutics).

much as 31% at high doses. Importantly, renal blood flow decreased 13%–37% at the same doses. Mesenteric blood flow decreased 32%–46%. High dose methoxamine, which increased MAP by 55%, produced a trend towards reduced coronary blood flow.[41]

Nygren et al. compared phenylephrine with norepinephrine (dosed to increase MAP by 30% for 30 minutes) in patients at the end of coronary artery bypass graft surgery, and found a larger increase in arterial lactate, splanchnic oxygen extraction, and mixed venous–hepatic vein saturation gradient in the phenylephrine group, suggesting that both global and gastrointestinal organ perfusion were relatively decreased in the phenylephrine group.[88]

CONCLUSIONS

In both animal and human studies, the effect of α_1 AR agonists on global CO depends on dosing as well as the complex interplay between the arterial and venous vasculature of both the pulmonary and systemic systems. α_1 AR agonists have the potential to both increase and decrease CO, the former via venoconstriction and conversion of unstressed to stressed volume (thus increasing preload), the latter by restriction of venous return (thus decreasing preload). Except in cases of myocardial failure or impaired autoregulation, the effects of α_1 AR agonists on CO are mediated predominantly by interactions with the venous system, whereas the effects of α_1 AR agonists on mVO_2 are mediated predominantly by interactions with the arterial system and the resultant increases in pressure work. At most doses studied (and used clinically), α_1 AR agonists tend to reduce CO and increase blood pressure, myocardial work, and oxygen requirements, which may be associated with myocardial injury. In the experimental setting, they have not been shown to increase blood flow in any organ system, and may significantly decrease coronary perfusion, although their effects on individual organs vary substantially.

REFERENCES

1. Hardman JG. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 9th ed. New York: McGraw-Hill, 1996
2. Appleton C, Olajos M, Morkin E, Goldman S. Alpha-1 adrenergic control of the venous circulation in intact dogs. J Pharmacol Exp Ther 1985;233:729–34
3. Landzberg JS, Parker JD, Gauthier DF, Colucci WS. Effects of myocardial alpha 1-adrenergic receptor stimulation and blockade on contractility in humans. Circulation 1991;84:1608–14
4. Curiel R, Perez-Gonzalez J, Brito N, Zerpa R, Tellez D, Cabrera J, Curiel C, Cubeddu L. Positive inotropic effects mediated by alpha 1 adrenoceptors in intact human subjects. J Cardiovasc Pharmacol 1989;14:603–15
5. Yang HT, Endoh M. Dissociation of the positive inotropic effect of methoxamine from the hydrolysis of phosphoinositide in rabbit ventricular myocardium: a comparison with the effects of phenylephrine and the subtype of the alpha-1 adrenoceptor involved. J Pharmacol Exp Ther 1994;269:732–42
6. Zimmerman BG, Abboud FM, Eckstein JW. Comparison of the effects of sympathomimetic amines upon venous and total vascular resistance in the foreleg of the dog. J Pharmacol Exp Ther 1963;139:290–5
7. Craig CR, Stitzel RE. Modern Pharmacology With Clinical Applications. Philadelphia: Lippincott Williams & Wilkins, 2003
8. Dart RC. Medical Toxicology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2003
9. Hensley FA, Martin DE, Gravlee GP. A Practical Approach to Cardiac Anesthesia. 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2007
10. Heath P, Geiter CW. Use of phenylephrine hydrochloride, neo-synephrine hydrochloride, in ophthalmology. Arch Ophthal 1949;41:172–7
11. Funk DJ, Moretti EW, Gan TJ. Minimally invasive cardiac output monitoring in the perioperative setting. Anesth Analg 2009;108:887–97
12. Magder S, Veerassamy S, Bates JH. A further analysis of why pulmonary venous pressure rises after the onset of LV dysfunction. J Appl Physiol 2009;106:81–90
13. Barcroft H, Edholm OG, McMichael J, Sharpey-Schafer EP. Posthaemorrhagic fainting: study by cardiac output and forearm flow. Lancet 1944;243:489–91
14. Puri GD, Marudhachalam KS, Chari P, Suri RK. The effect of magnesium sulphate on hemodynamics and its efficacy in attenuating the response to endotracheal intubation in patients with coronary artery disease. Anesth Analg 1998;87:808–11
15. Boyce W. Elementary Differential Equations and Boundary Value Problems. 6th ed. New York: Wiley, 1997
16. Wang JJ, Flewitt JA, Shrive NG, Parker KH, Tyberg JV. Systemic venous circulation. Waves propagating on a windkessel: relation of arterial and venous windkessels to systemic vascular resistance. Am J Physiol Heart Circ Physiol 2006;290:H154–62
17. Frank O. Die Grundform des arteriellen Pulses. Zeitung fuŕ Biologie 1899;37:483–586

18. O'Rourke MF, Avolio AP. Pulsatile flow and pressure in human systemic arteries. Studies in man and in a multibranched model of the human systemic arterial tree. Circ Res 1980;46:363–72
19. Gelman S. Venous function and central venous pressure: a physiologic story. Anesthesiology 2008;108:735–48
20. Greenway CV, Lautt WW. Blood volume, the venous system, preload, and cardiac output. Can J Physiol Pharmacol 1986;64:383–7
21. Quick CM, Berger DS, Noordergraaf A. Apparent arterial compliance. Am J Physiol 1998;274:H1393–403
22. Essler S, Schroeder MJ, Phaniraj V, Koenig SC, Latham RD, Ewert D. Fast estimation of arterial vascular parameters for transient and steady beats with application to hemodynamic state under variant gravitational conditions. Ann Biomed Engl 1999;27:486–97
23. O'Rourke MF. The arterial pulse in health and disease. Am Heart J 1971;82:687–702
24. Kelly RP, Tunin R, Kass DA. Effect of reduced aortic compliance on cardiac efficiency and contractile function of in situ canine left ventricle. Circ Res 1992;71:490–502
25. Rothe CF. Reflex control of veins and vascular capacitance. Physiol Rev 1983;63:1281–342
26. Guyton AC. Determination of cardiac output by equating venous return curves with cardiac response curves. Physiol Rev 1955;35:123–9
27. Maas JJ, Geerts BF, van den Berg PC, Pinsky MR, Jansen JR. Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients. Crit Care Med 2009;37:912–8
28. Magder S. The classical Guyton view that mean systemic pressure, right atrial pressure, and venous resistance govern venous return is/is not correct. J Appl Physiol 2006;101:1533
29. van den Berg PC, Jansen JR, Pinsky MR. Effect of positive pressure on venous return in volume-loaded cardiac surgical patients. J Appl Physiol 2002;92:1223–31
30. Levy MN. The cardiac and vascular factors that determine systemic blood flow. Circ Res 1979;44:739–47
31. Tyberg JV. How changes in venous capacitance modulate cardiac output. Pflugers Arch 2002;445:10–7
32. Flamm SD, Taki J, Moore R, Lewis SF, Keech F, Maltais F, Ahmad M, Callahan R, Dragotakes S, Alpert N, Strauss W. Redistribution of regional and organ blood volume and effect on cardiac function in relation to upright exercise intensity in healthy human subjects. Circulation 1990;81:1550–9
33. Brengelmann GL. Counterpoint: the classical Guyton view that mean systemic pressure, right atrial pressure, and venous resistance govern venous return is not correct. J Appl Physiol 2006;101:1525–6
34. Magder S. Point: the classical Guyton view that mean systemic pressure, right atrial pressure, and venous resistance govern venous return is/is not correct. J Appl Physiol 2006;101:1523–5
35. Guyton AC, Lindsey AW, Abernathy B, Richardson T. Venous return at various right atrial pressures and the normal venous return curve. Am J Physiol 1957;189:609–15
36. Guyton AC, Abernathy B, Langston JB, Kaufmann BN, Fairchild HM. Relative importance of venous and arterial resistances in controlling venous return and cardiac output. Am J Physiol 1959;196:1008–14
37. Nichols WW, Pepine CJ. Left ventricular afterload and aortic input impedance: implications of pulsatile blood flow. Prog Cardiovasc Dis 1982;24:293–306
38. O'Rourke MF, Yaginuma T, Avolio AP. Physiological and pathophysiological implications of ventricular/vascular coupling. Ann Biomed Engl 1984;12:119–34
39. Hangai K, Satoh S, Sato F, Watanabe J, Maruyama Y, Takishima T. Continuous measurement of canine coronary blood volume change with alterations of heart rate. Cardiovasc Res 1993;27:1127–34
40. O'Rourke MF. Vascular impedance in studies of arterial and cardiac function. Physiol Rev 1982;62:570–623
41. Heyndrickx GR, Boettcher DH, Vatner SF. Effects of angiotensin, vasopressin, and methoxamine on cardiac function and blood flow distribution in conscious dogs. Am J Physiol 1976;231:1579–87
42. Woodman OL, Vatner SF. Coronary vasoconstriction mediated by alpha 1- and alpha 2-adrenoceptors in conscious dogs. Am J Physiol 1987;253:H388–93
43. Crystal GJ, Kim SJ, Salem MM, Abdel-Latif M. Myocardial oxygen supply/demand relations during phenylephrine infusions in dogs. Anesth Analg 1991;73:283–8
44. Miller RR, Awan NA, DeMaria AN, Amsterdam EA, Mason DT. Importance of maintaining systemic blood pressure during nitroglycerin administration for reducing ischemic injury in patients with coronary disease. Effects on coronary blood flow, myocardial energetics and left ventricular function. Am J Cardiol 1977;40:504–8
45. Rudner XL, Berkowitz DE, Booth JV, Funk BL, Cozart KL, D'Amico EB, El-Moalem H, Page SO, Richardson CD, Winters B, Marucci L, Schwinn DA. Subtype specific regulation of human vascular alpha(1)-adrenergic receptors by vessel bed and age. Circulation 1999;100:2336–43
46. Loeb HS, Saudye A, Croke RP, Talano JV, Klodnycky ML, Gunnar RM. Effects of pharmacologically-induced hypertension on myocardial ischemia and coronary hemodynamics in patients with fixed coronary obstruction. Circulation 1978;57:41–6
47. Antonopoulos A, Nikolopoulos D, Georgiou EK, Kyriakidis M, Proukakis C. Blood pressure elevation after phenylephrine infusion may adversely affect myocardial perfusion in patients with coronary artery disease. Int J Cardiol 2002;84:201–9
48. Lang RM, Borow KM, Neumann A, Janzen D. Systemic vascular resistance: an unreliable index of left ventricular afterload. Circulation 1986;74:1114–23
49. Strauer BE, Beer K, Heitlinger K, Hofling B. Left ventricular systolic wall stress as a primary determinant of myocardial oxygen consumption: comparative studies in patients with normal left ventricular function, with pressure and volume overload and with coronary heart disease. Basic Res Cardiol 1977;72:306–13
50. Langesaeter E, Rosseland LA, Stubhaug A. Continuous invasive blood pressure and cardiac output monitoring during cesarean delivery: a randomized, double-blind comparison of low-dose versus high-dose spinal anesthesia with intravenous phenylephrine or placebo infusion. Anesthesiology 2008; 109:856–63
51. Brooker RF, Butterworth JFT, Kitzman DW, Berman JM, Kashtan HI, McKinley AC. Treatment of hypotension after hyperbaric tetracaine spinal anesthesia. A randomized, double-blind, cross-over comparison of phenylephrine and epinephrine. Anesthesiology 1997;86:797–805
52. Sharrock NE, Go G, Mineo R, Harpel PC. The hemodynamic and fibrinolytic response to low dose epinephrine and phenylephrine infusions during total hip replacement under epidural anesthesia. Thromb Haemost 1992;68:436–41
53. Asanoi H, Kameyama T, Ishizaka S, Nozawa T, Inoue H. Energetically optimal left ventricular pressure for the failing human heart. Circulation 1996;93:67–73
54. Barash PG, Cullen BF, Stoelting RK. Clinical Anesthesia. 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2005
55. Suga H, Hisano R, Goto Y, Yamada O, Igarashi Y. Effect of positive inotropic agents on the relation between oxygen consumption and systolic pressure volume area in canine left ventricle. Circ Res 1983;53:306–18
56. Suga H. Ventricular energetics. Physiol Rev 1990;70:247–77
57. Suga H, Yamada O, Goto Y. Energetics of ventricular contraction as traced in the pressure-volume diagram. Fed Proc 1984;43:2411–3
58. Suga H, Hayashi T, Shirahata M. Ventricular systolic pressure-volume area as predictor of cardiac oxygen consumption. Am J Physiol 1981;240:H39–44
59. Suga H, Igarashi Y, Yamada O, Goto Y. Cardiac oxygen consumption and systolic pressure volume area. Basic Res Cardiol 1986;81(suppl 1):39–50

60. Khalafbeigui F, Suga H, Sagawa K. Left ventricular systolic pressure-volume area correlates with oxygen consumption. Am J Physiol 1979;237:H566–9
61. Burkhoff D, Yue DT, Oikawa RY, Franz MR, Schaefer J, Sagawa K. Influence of ventricular contractility on non-work-related myocardial oxygen consumption. Heart Vessels 1987;3:66–72
62. Cassidy SC, McGovern JJ, Chan DP, Allen HD. Effects of commonly used adrenergic agonists on left ventricular function and systemic vascular resistance in young piglets. Am Heart J 1997;133:174–83
63. Smith JS, Roizen MF, Cahalan MK, Benefiel DJ, Beaupre PN, Sohn YJ, Byrd BF, Schiller NB, Stoney RJ, Ehrenfeld WK, Ellis JE, Aronson S. Does anesthetic technique make a difference? Augmentation of systolic blood pressure during carotid endarterectomy: effects of phenylephrine versus light anesthesia and of isoflurane versus halothane on the incidence of myocardial ischemia. Anesthesiology 1988;69:846–53
64. Goertz AW, Schmidt M, Seefelder C, Lindner KH, Georgieff M. The effect of phenylephrine bolus administration on left ventricular function during isoflurane-induced hypotension. Anesth Analg 1993;77:227–31
65. Goertz AW, Lindner KH, Seefelder C, Schirmer U, Beyer M, Georgieff M. Effect of phenylephrine bolus administration on global left ventricular function in patients with coronary artery disease and patients with valvular aortic stenosis. Anesthesiology 1993;78:834–41
66. Stewart A, Fernando R, McDonald S, Hignett R, Jones T, Columb M. The dose-dependent effects of phenylephrine for elective cesarean delivery under spinal anesthesia. Anesth Analg 2010;111:1230–7
67. Eichler HG, Ford GA, Blaschke TF, Swislocki A, Hoffman BB. Responsiveness of superficial hand veins to phenylephrine in essential hypertension. Alpha adrenergic blockade during prazosin therapy. J Clin Invest 1989;83:108–12
68. Hirakawa S, Itoh H, Kotoo Y, Abe C, Endo T, Takada N, Fuseno H. The role of alpha and beta adrenergic receptors in constriction and dilation of the systemic capacitance vessels: a study with measurements of the mean circulatory pressure in dogs. Jpn Circ J 1984;48:620–32
69. Pang CC. Autonomic control of the venous system in health and disease: effects of drugs. Pharmacol Ther 2001;90:179–230
70. Butterworth, JF. Do alpha agonists increase venous return? Anesthesiology 2004;101:1039
71. Rothe CF. Mean circulatory filling pressure: its meaning and measurement. J Appl Physiol 1993;74:499–509
72. Gelman S, Mushlin PS. Catecholamine-induced changes in the splanchnic circulation affecting systemic hemodynamics. Anesthesiology 2004;100:434–9
73. Zandberg P, Timmermans PB, van Zwieten PA. Hemodynamic profiles of methoxamine and B-HT 933 in spinalized ganglion-blocked dogs. J Cardiovasc Pharmacol 1984;6:256–62
74. Marino RJ, Romagnoli A, Keats AS. Selective venoconstriction by dopamine in comparison with isoproterenol and phenylephrine. Anesthesiology 1975;43:570–2
75. Tuman KJ, McCarthy RJ, March RJ, Guynn TP, Ivankovich AD. Effects of phenylephrine or volume loading on right ventricular function in patients undergoing myocardial revascularization. J Cardiothorac Vasc Anesth 1995;9:2–8
76. Harik SI, Sharma VK, Wetherbee JR, Warren RH, Banerjee SP. Adrenergic and cholinergic receptors of cerebral microvessels. J Cereb Blood Flow Metab 1981;1:329–38
77. Peroutka SJ, Moskowitz MA, Reinhard JF Jr., Snyder SH. Neurotransmitter receptor binding in bovine cerebral microvessels. Science 1980;208:610–2
78. Kobayashi H, Wada A, Izumi F, Magnoni MS, Trabucchi M. Alpha-adrenergic receptors in cerebral microvessels of normotensive and spontaneously hypertensive rats. Circ Res 1985;56:402–9
79. Mizuki T, Kobayashi H, Ueno S, Nakashima Y, Kuroiwa A, Izumi F. Differential changes in alpha- and beta-adrenoceptors in the cerebral cortex and hippocampus of the Mongolian gerbil after unilateral brain ischemia. Stroke 1995;26:2333–7
80. O'Neill C, Fowler CJ, Winblad B. Alpha 1-adrenergic receptor binding sites in post-mortal human cerebral microvessel preparations: preservation in multi-infarct dementia and dementia of Alzheimer type. J Neural Transm Park Dis Dement Sect 1989;1:303–10
81. Cho S, Fujigaki T, Uchiyama Y, Fukusaki M, Shibata O, Sumikawa K. Effects of sevoflurane with and without nitrous oxide on human cerebral circulation. Transcranial Doppler study. Anesthesiology 1996;85:755–60
82. Smrcka M, Ogilvy CS, Crow RJ, Maynard KI, Kawamata T, Ames A 3rd. Induced hypertension improves regional blood flow and protects against infarction during focal ischemia: time course of changes in blood flow measured by laser Doppler imaging. Neurosurgery 1998;42:617–24
83. Kitaguchi K, Ohsumi H, Kuro M, Nakajima T, Hayashi Y. Effects of sevoflurane on cerebral circulation and metabolism in patients with ischemic cerebrovascular disease. Anesthesiology 1993;79:704–9
84. Joseph M, Ziadi S, Nates J, Dannenbaum M, Malkoff M. Increases in cardiac output can reverse flow deficits from vasospasm independent of blood pressure: a study using xenon computed tomographic measurement of cerebral blood flow. Neurosurgery 2003;53:1044–51
85. Grangsjo G, Persson E. Influence of some vaso-active substances on regional blood flow in the dog kidney. A study on normovolaemic and hypovolaemic dogs. Acta Anaesthesiol Scand 1971;15:71–95
86. Shinomiya K, Kajima M, Tajika H, Shiota H, Nakagawa R, Saijyou T. Renal failure caused by eyedrops containing phenylephrine in a case of retinopathy of prematurity. J Med Invest 2003;50:203–6
87. Hoffbrand BI, Forsyth RP. Regional blood flow changes during norepinephrine, tyramine and methoxamine infusions in the unanesthetized rhesus monkey. J Pharmacol Exp Ther 1973;184:656–61
88. Nygren A, Thoren A, Ricksten SE. Vasopressors and intestinal mucosal perfusion after cardiac surgery: Norepinephrine vs. phenylephrine. Crit Care Med 2006;34:722–9