Concise Definitive Review

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The Role of Venous Return in Critical Illness and Shock—Part I: Physiology

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Objective: To provide a conceptual and clinical review of the physiology of the venous system as it is relates to cardiac function in health and disease.

Data: An integration of venous and cardiac physiology under normal conditions, critical illness, and resuscitation.

Summary: The usual teaching of cardiac physiology focuses on left ventricular function. As a result of the wide array of shock states with which intensivists contend, an approach that takes into account the function of the venous system and its interaction with the right and left heart may be more useful. This two-part review focuses on the function of the venous system and right heart under normal and stressed conditions. The first part describes the basic physiology of the venous system, and part two focuses on the role of the venous system in different pathophysiologic states, particularly shock.

Conclusion: An improved understanding of the role of the venous system in health and disease will allow intensivists to better appreciate the complex circulatory physiology of shock and may allow for better hemodynamic management of this disorder. (*Crit Care Med* 2013; 41:255–262)

Key Words: cardiogenic shock; cardiovascular physiology; hemodynamics; hemorrhagic shock; obstructive shock; septic shock

In the modern era, the typical hemodynamic analysis of cardiovascular function focuses on left ventricular (LV) physiology. The reason for this is the primacy of ischemic heart disease (which most obviously affects LV function) as a cause of death in the developed world as well as the complex pathophysiology of the right ventricle (RV)/venous system, which results in practical difficulties in assessing RV/venous performance in the critically ill. An approach that centers on LV function is appropriate for most cardiologists given their focus on management of myocardial infarction and congestive heart failure. However, intensivists deal with a broader array of cardiovascular perturbations including shock states in which vascular dysfunction and other extracardiac perturbations may dominate the clinical picture (e.g., septic, hypovolemic, or obstructive shock). An approach to cardiovascular physiology that incorporates both cardiac and vascular elements may be more useful to intensivists than one that focuses exclusively on LV physiology.

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This two-part review discusses the role of the heart and venous system in regulating venous return (VR) and cardiac output (CO). The primary determinants of VR are explained and alterations in VR in different pathophysiologic states are described. In the second part of this review, the physiology of VR is graphically integrated with RV physiology in the context of a variety of pathophysiologic states including shock. In addition, the effects of common therapies for the shock states (fluid administration, vasopressor and inotropic support, and mechanical ventilation) are examined in relation to their impact on VR and CO interactions.

FUNCTION OF THE VENOUS SYSTEM

The main functions of the systemic venous system are to act as a conduit to return blood to the heart from the periphery and to serve as a reservoir of the circulating blood volume. Although the cardiovascular circuit is a two-compartment model comprising both a systemic and pulmonary circuit, >80% of the blood volume held in veins is in the systemic venous circulation with three fourths of that in small veins and venules (1, 2) (**Table 1**). The pulmonary veins contain only a small blood volume and left atrial pressure has a relatively modest effect on left heart function. For these reasons, the physiology of VR can be described, in practical terms, as the physiology of VR to the heart.

Veins have a compliance 30 times greater than arteries and contain approximately 70% of the total blood volume compared with only 18% for the arteries (3–5). Because of the

TABLE 1. Distribution of Blood in the Various Components of the Circulatory System

Structure	Percentage of Total Blood Volume
Systemic venous system	64
Systemic arterial system	13
Capillaries	7
Pulmonary circuit	9
Heart	7

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high compliance of veins, large changes in blood volume are not associated with significant changes in venous transmural pressure. These features make the venous system an ideal blood reservoir that can maintain filling of the right heart despite significant variations in circulatory volume. The veins of the splanchnic bed alone hold approximately 20% to 33% of the total blood volume (6, 7).

Hagen-Poiseuille's law is central to the understanding of both VR and CO. This law (analogous to Ohm's law of electrical current flow) states that the fluid flow (Q) through a system (such as the cardiovascular circuit) is related to the pressure drop across the system divided by the resistance of the system:

$$\dot{Q} = \frac{P_1 - P_2}{R}$$

where P_1 is upstream pressure, P_2 is downstream pressure, and R is resistance to flow.

Left heart output (i.e., CO) and flow through the systemic circulation are commonly described using a variation of Hagen-Poiseuille's law. The difference between mean arterial pressure (MAP [P_1]) and right atrial pressure (P_{RA} [P_2]) is the pressure drop across the system and systemic vascular resistance (SVR) represents resistance to flow through the circuit:

$$CO = \frac{MAP - P_{RA}}{SVR}$$

Because CO must equal VR, it is intuitive that VR to the right heart can be similarly described:

$$VR = \frac{P_{ms} - P_{RA}}{R_v}$$

where P_{ms} is the mean systemic pressure of the circulation and R_V is the resistance to VR. The P_{ms} is the upstream pressure for the venous circulation, whereas P_{RA} is again the downstream pressure (as it is in the equation describing systemic blood flow). This equation represents the application of Hagen-Poiseuille's law to the venous circulation. Note that this conceptual framework suggests that arterial pressure is unrelated to VR and that the flow into the systemic arterial circuit is only relevant insofar as it is required to maintain the volume of the venous reservoir. The concept of P_{ms} is described more fully subsequently.

Note that resistance to flow in both equations (SVR and R_v) is directly proportional to the length of the blood vessels (l), the viscosity of blood (η), and it is inversely proportional to the radius (r) of the vessels to the fourth power. Mathematically:

$$R = \frac{8nl}{\pi r^4}$$

In most pathophysiologic analyses, the radius and length of the conduit are emphasized in the assessment of resistance to flow; viscosity is ignored. However, in clinical settings, liters of low-viscosity (relative to whole blood) crystalloid or colloids may be administered over short periods. Furthermore, priming a cardiopulmonary bypass or extracorporeal membrane oxygenation circuit also involves administration of large amounts of low viscosity fluids. In these settings, alterations in blood viscosity resulting from hemodilution may provide a significant contribution to changes in resistance (8, 9).

Although the most common theoretical construct of cardiac function used by clinicians suggests that the left heart plays a major role in the regulation of CO (three of the four determinants of left heart CO, that is, preload, heart rate, and contractility, are intrinsically cardiac-related indices), the VR equation suggests cardiac function plays only an indirect role in the governance of VR. The only way that cardiac function can affect VR is by altering P_{RA} and thereby changing the driving pressure gradient. As a consequence of the normal modest operating range of pressures in the venous circuit (8–12 mm Hg in venules to 1–2 mm Hg in the vena cava/right atrium) (10), small changes in P_{RA} can drive very large changes in VR. Given that CO and VR must be equal in a closed system, the obvious corollary is that CO, under most physiological and pathophysiological conditions, is not primarily dependent on LV cardiac function, but on VR to the right heart.

Further to this issue, CO/VR is, in fact, determined by the interaction of the heart as a whole (inclusive of the right heart, pulmonary circuit, and left heart characteristics) with the systemic vascular circuit, not by any individual element. The elements contributing to cardiac function in this context include the loads on and compliance of the right and left ventricles and the compliance and resistance of the pulmonary circuit. For the sake of simplicity, our subsequent discussion often focuses on right heart function but it should be understood that right heart function in this context represents an amalgam of all influences on the heart as a whole.

To appreciate VR physiology, three related factors must be appreciated: the concepts of P_{ms}, stressed and unstressed volumes, and venous resistance (Rv). The concept of P_{ms} dates back to the late 1800s when Bayliss and Starling surmised that if the circulation was transiently halted, arterial pressure would fall and venous pressure would rise (11). They reasoned that the pressure in the entire system during cardiac standstill would equilibrate at what they termed P_{ms}. After blood in the circulatory system started flowing again, upstream (arterial) pressure would rise and downstream (venous) pressure would

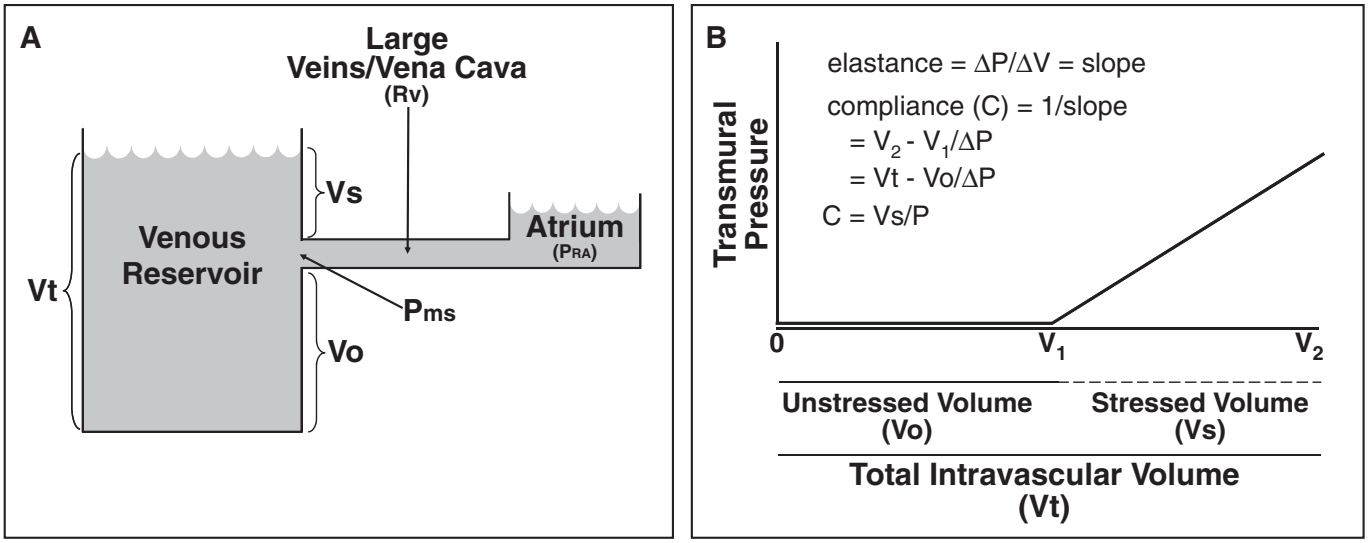

Figure 1. **A**, Concept of stressed and unstressed blood volume. The volume within the main container represents the systemic venous blood volume (V_t) and the level of the opening of the outflow conduit divides V_t into stressed volume (V_s) above and unstressed volume (V_o) below the level of the conduit. Only V_s (i.e., volume above the conduit level) contributes to the outflow driving pressure (analogous to mean systemic pressure [P_{ms}]) at the conduit. The blood leaves the container at a rate that is dependent in part on the pressure (P_{ms}) exerted by the fluid above the opening (i.e., V_s). The blood below the opening (i.e., V_o) does not affect the outflow pressure or flow. Moving the entrance to the conduit down increases Vs and the outflow pressure (without changing V_t) resulting in greater flow out of the tub. In contrast, increasing the total volume without moving the conduit opening increases V_t in addition to V_s, outflow pressure, and flow. In the body, increasing V_s in the cardiovascular circuit by either altering the relative proportions of blood volume (V_s vs. V_o) or adding to V_t with fluids will increase outflow pressure (P_{ms}) and venous return. Right atrial pressure (P_{RA}) represents the downstream pressure and the outflow conduit diameter and length as well as blood viscosity define resistance to venous return (R_v). Adapted from Bressack MA, Raffin TA: Importance of venous return, venous resistance, and mean circulatory pressure in the physiology and management of shock. *Chest* 1987; 92:906–912. **B**, Graphic representation of V_s, V_o, and V_t in relation to vascular compliance (C) and vascular transmural pressure (i.e., P_{ms}). If the container is empty and the volume in the container and the pressure (at the level of the conduit) are graphically displayed, slow replacement of the fluid would result in a linear increase in volume but pressure would remain flat until the pressure transducer at the level of the conduit opening was submerged. Thereafter, the pressure would increase linearly to the limit of filling of the container. The slope of the line between V_2 and V_1 (defining stressed volume) would represent elastance ($E = \Delta P/\Delta V$). Elastance is the inverse of compliance so compliance would be defined as $C = \Delta V/\Delta P$. However, ΔV is stressed volume ($V_s = V_2 - V_1 = V_t - V_o$) and the transmural pressure is analogous to P_{ms}. Compliance is equivalent to $V_t - V_o/P_{ms}$. A simple rearrangement produces the equation defining P_{ms} in the text. P = pressure; ΔP = change in pressure; ΔV = change in volume. See text for further explanation.

fall as a consequence of the pumping action of the heart. However, the average pressure across the system would be the same as when it was at rest (i.e., P_{ms}). Bayliss and Starling further reasoned that a point in the circulation that was equal to the P_{ms} during active flow had to lie on the venous side of the circulation because of its higher capacitance. They also determined that P_{ms} must be independent of MAP because it could be defined in the absence of cardiac pump function. As a consequence, P_{ms} is understood to represent the upstream pressure (P1 in Poiseuille's law) supporting VR. The P_{RA}, which is usually understood as a measure of right ventricular preload (and a key determinant of increased CO), represents the downstream resistive pressure to VR (P2 in Poiseuille's Law) in this model.

The value of P_{ms} in the body is described by the equation:

$$P_{ms} = Vs/Csw$$

where Vs is stressed blood volume and C is systemic compliance (mean compliance of the cardiovascular circuit). The latter approximates the compliance of the venous reservoir.

Unstressed intravascular volume can be defined as that volume required to fill the circulatory system to capacity without any increase in transmural pressure (2). Stressed volume would be that amount that, when added to the unstressed volume, generates the vascular transmural pressure. To grasp the concept of stressed and unstressed volumes in the circulatory system, it is helpful to understand that only a portion of the total blood volume (Vt) contributes to the residual pressure (i.e., P_{ms}) in the circulation during cardiac standstill. Passive exsanguination of an anticoagulated experimental animal would result in a large blood loss. The external, exsanguinated volume would represent the stressed blood volume (Vs). The amount remaining in the circulation would be the unstressed volume (Vo).

Figures 1*A* and **1*B*** illustrate these concepts. As discussed in the figure legend, the equation for P_{ms} can be written as:

$$P_{ms} = \frac{V_t - V_o}{C}$$

This equation suggests that P_{ms} can be altered through two basic mechanisms: (1) a change in the total volume in the reservoir (Vt); or (2) a change in the proportion of Vo and Vs (5). Under ideal circumstances, adding or removing volume should increase and decrease Vt and Vs, respectively, without altering Vo. An alteration of autonomic tone, catecholamine stress responses, or infusion of exogenous vasoactive substances will alter the ratio of Vs to Vo without a change in C (12–14). Although some formulations suggest that compliance is directly altered by sympathetic stimulation, compliance in

the model should be considered to be an aggregate static (i.e., passive) mechanical property of the vessel walls (2, 7).

Approximately 20% to 30% (approximately 1.5 L) of a typical human's total blood volume is stressed volume (6). Under normal conditions, human P_{ms} has been measured at approximately 8–10 mm Hg (15–17). With that information, the compliance of the human vascular bed can be calculated to be ~0.187 L·mm Hg^{-1} (18–22). Absent autonomic influences, infusion of 1 L of fluid would therefore raise the P_{ms} by 5.3 mm Hg (1 L/0.187 L·mm Hg^{-1}).

The denominator in the equation for VR, the resistance to VR or R_V, is the other major concept that must be explored. The same basic determinants of resistance that apply for the SVR also apply to R_v, that is, R_v is directly proportional to the length of the venous circuit and the blood viscosity and is inversely related to the fourth power of the mean radius (r^4).

The R_V depends on the resistance and capacitance of the different portions of the peripheral circulation. The cross-sectional area and radius of the venous system varies tremendously between the venules and small veins as compared with the large veins and vena cava. This division effectively creates two compartments. The small veins and venules with a very large cross-sectional area contribute little to Rv and primarily serve as the venous reservoir. The cross-sectional area of the vena cava and large veins is small; these vessels act primarily as a conduit and account for the large majority of venous resistance (R_v). They make a relatively small contribution to the volume of the venous reservoir. Increased autonomic tone or administration of vasopressor compounds creates countervailing effects in increased stressed volume and P_{ms} in the reservoir compartment (which increases VR) but decreased mean radius in the vena cava and large veins (which decreases VR). Decreases in autonomic tone and vasodilators have the opposite effect.

The effective length of the venous circulation through which blood passes also affects Rv. The venous system is not a system of uniform length and volume of veins and venules. Some parts of the venous system have longer, slower paths for flow, whereas others are shorter and faster. This has been described as short- and long-time constant beds (23, 24). The time constant, or τ, of a vascular bed is determined by the volume of the bed divided by the flow through it. Among vascular beds with varying time constants, the renal vascular bed has a low volume but rapid flow, giving it a fast time constant, or τ_f. In contrast, the skin has a large volume and slow flow, giving it a slow time constant, or τ_s. The fraction of blood distributed between these tissue beds with fast and slow time constants is called F_f and F_s, respectively. Autonomic alterations/endogenous factors and exogenous vasoactive substances, in addition to generating changes in Vs of the venous reservoir and cross-sectional area of the venous circuit, can also result in redistribution of venous flow between long-time constant and short-time constant beds. A redistribution of blood from predominantly τ_s to τ_f will have the effect of reducing R_v and increasing VR.

Blood viscosity has usually been considered to have negligible effects on VR and CO in most analyses. However, recent evidence suggests that the modest increases in VR/CO associated with crystalloid infusion are generated, in part, through reductions in blood viscosity (resulting in decreased Rv) in addition to any effects on P_{ms} (9).

Although VR is determined by P_{ms}, P_{RA}, and R_v over a wide variety of physiologic and pathophysiologic conditions, VR is also limited by the mechanics of the respiratory system. Within the thorax, the heart and vascular structures are exposed to pleural pressure (P_{PL}) that varies with the respiratory cycle. Outside of the thorax, veins are exposed to relatively constant pressures within the body compartments that approximate (under normal conditions) atmospheric pressure (P_{atm}). Normally, P_{RA} exceeds P_{PL} and represents the downstream opposing pressure to flow in the numerator of the VR equation ($P_{ms} - P_{RA}$). However, during inspiration, P_{PL} becomes increasingly negative. This negative pleural (intrathoracic) pressure is transmitted to the right heart circuit. As a consequence, venous pressures and P_{RA} may transiently fall below P_{atm}. Because the major extrathoracic veins are surrounded by body compartment pressures that normally approximate P_{atm}, they collapse at the point where they enter the thoracic cavity and then act as Starling resisters (25, 26). Effectively, P_{atm} becomes the downstream pressure opposing venous flow in the numerator of the VR equation ($P_{ms} - P_{atm}$). Blood flow instantaneously and transiently ceases. As flow is halted, the pressure in the proximal thoracic veins and vena cava rapidly rises until it equilibrates with P_{ms} and the veins open again (because P_{ms} is greater than P_{atm}) and flow is re-established. This sequence cycles rapidly limiting flow during inspiration until positive intrathoracic pressures are re-established with expiration. Then with the next inspiration, the entire cycle repeats itself. As a consequence of this effect, VR reaches a plateau when the transmural P_{RA} is 0 mm Hg (i.e., atmospheric pressure) in the spontaneously breathing subject.

The graphical representation of the equation for VR is depicted in **Figure 2**. VR is maximal when the P_{RA} (the downstream pressure) is 0 mm Hg and the gradient between P_{ms} and P_{RA} is greatest. If P_{RA} falls below 0 mm Hg, flow is limited by the collapse of the extrathoracic veins (as described previously), and VR remains at a plateau. VR falls as P_{RA} increases. According to the equation for VR ($VR = P_{ms} - P_{RA}/R_v$), VR can only be 0 when there is no pressure gradient ($P_{ms} - P_{RA} = 0$). This occurs at the intersection of the VR curve with the abscissa (horizontal axis), VR = 0.

The slope of the portion of the VR curve at $P_{RA} > 0$ (i.e., the diagonal portion of the VR curve) represents the difference in flow (VR) divided by the pressure differential at different points of P_{RA} (i.e., slope = Q/P). Because resistance is, by definition, driving pressure divided by flow (P/Q), the inverse of the slope of the VR curve represents R_V (equations shown in Fig. 2).

Effect of Different Circulatory Manipulations on VR

There are a limited number of ways to change VR. Manipulating either P_{ms} (and its constitutive factors Vt, Vs, and Vo) and/or resistance to VR (R_v) will lead to changes in the shape and position of the VR curves.

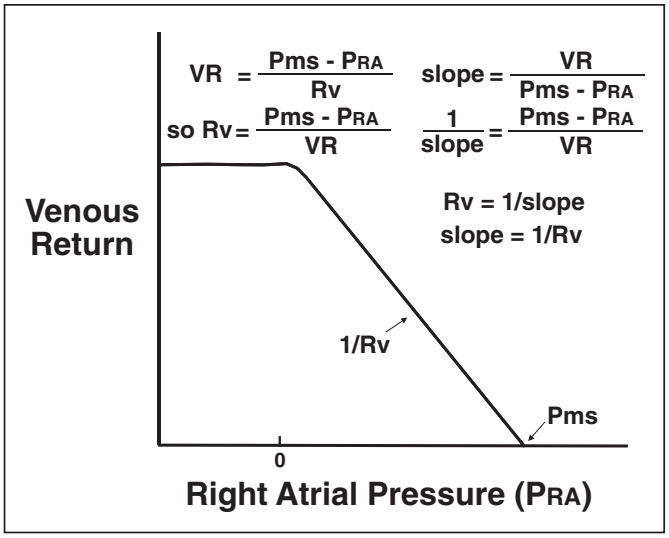

Figure 2. Venous return (VR) curve. The intersection of the curve with the x-axis/abscissa represents the mean systemic pressure (P_{ms}) because it is at that point VR has a zero value. VR can only be zero if $P_{ms} - P_{RA}$ is zero (i.e., $P_{ms} = P_{RA}$). The equations on the top left of the figure rearrange the VR equation to define venous resistance (Rv). The equations on the top right define slope of the VR curve. Rv and the inverse of the slope of the VR curve can be shown to be defined by the same equation ($[P_{ms} - P_{RA}]$/VR) where P_{RA} is right atrial pressure. Therefore, slope is inversely related to Rv. VR is at its maximum with a right atrial pressure (P_{RA}) of 0 mm Hg as a result of the collapsibility of the intrathoracic veins. See text for additional explanation.

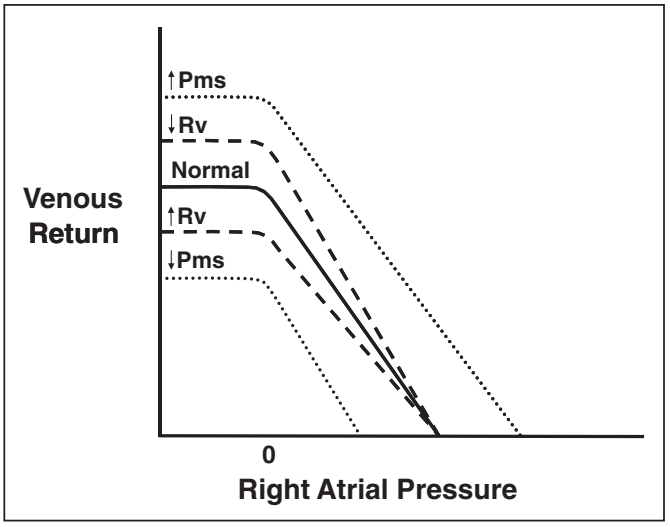

Figure 3. Effect of changes in mean systemic pressure (P_{ms}) and venous resistance (Rv) on venous return (VR). An increase in P_{ms} results in a rightward shift of the curve, whereas a decrease in P_{ms} causes a leftward shift of the curve (*dotted lines*). Increasing R_V results in a counterclockwise shift in the curve and a drop in VR (*dashed lines*). Conversely, decreases in R_V results in a clockwise shift of the curve and an increase in VR. See text for explanation.

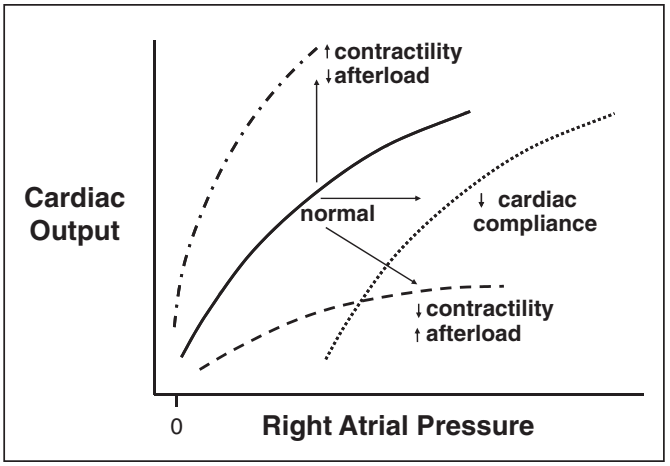

Figure 4. Starling cardiac function curves. Increased contractility or decreased afterload rotates the curve upward. Decreased contractility or increased afterload rotates the curve downward. Isolated diastolic dysfunction or decreased effective cardiac compliance causes a parallel and rightward shift of the curve. Note that figures are illustrative and drawn to optimally demonstrate the key concepts of this review. In particular, they are not meant to imply an absence of a plateau with increasing filling pressures.

Any change in P_{ms} alone leads to a shift in the intercept of the VR curve at the abscissa without any change in the slope of the curve (i.e., venous resistance unchanged) and with the inflection point of the plateau remaining constant at a transmural P_{RA} of 0 mm Hg (**Fig. 3**). An increase in P_{ms} shifts the curve to the right, increasing VR. This elevation of P_{ms} can be driven by an increase in Vt, whereas Vo remains fixed or an increase in the proportion of Vs relative to Vo. A decrease in P_{ms} generates a shift in the opposite direction (toward a decrease in VR). Any decrease in P_{ms} is caused by a decrease in Vt, whereas Vo remains fixed or a decrease in the ratio of Vs to Vo.

In contrast, an isolated change in R_v affects the slope of the VR curve without moving the intercept of the curve with the abscissa/x-axis (i.e., P_{ms} is constant) or the pressure at which the curve plateaus (Fig. 3). An increase in R_v produces a shallower slope, whereas a decrease in R_v generates a steeper slope. As seen in Figure 3, decreasing R_V causes an increase in VR for a fixed P_{RA}, whereas an increase in R_V for a fixed P_{RA} will cause a decrease in VR (27–29).

Cardiac Function and Its Relationship to VR

The curves discussed to this point describe a range of possible VR values under different conditions of the venous system (P_{ms} and Rv) and cardiac function (as reflected by P_{RA}). To define VR under any given condition, additional information is needed. The Starling response curve describes CO for any given level of cardiac filling (ventricular end-diastolic volume). A closely related, analogous cardiac function curve can be generated using ventricular end-diastolic pressure or P_{RA}. Although this analytic approach is usually applied to the left heart, the right ventricle operates on the same principle. The curve shifts upward with increased contractility or decreased afterload and downward with decreased contractility or increased afterload (**Fig. 4**). Isolated diastolic dysfunction (e.g., acute ischemia) or any decrease in effective cardiac compliance (e.g., in association with increased pericardial or intrathoracic pressure) causes a parallel rightward shift of the curve (Fig. 4). There is some ability of the right ventricle to increase its contractility with increases in RV afterload through homeometric autoregulation (also known as the Anrep

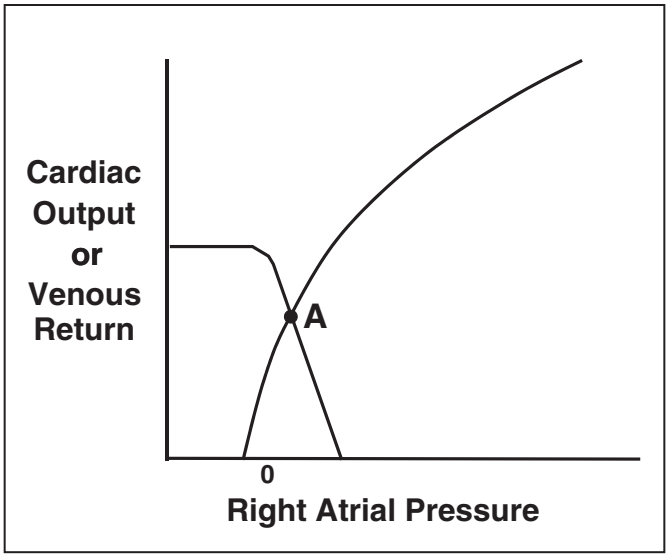

Figure 5. Venous return and cardiac output plotted on the same graph. At steady state, cardiac output and venous return must be identical and both are dependent on right atrial pressure/central venous pressure. This allows curves describing each to be superimposed. The intersection of the curves will define a common venous return/cardiac output under different conditions of venous and right heart function. See text for details.

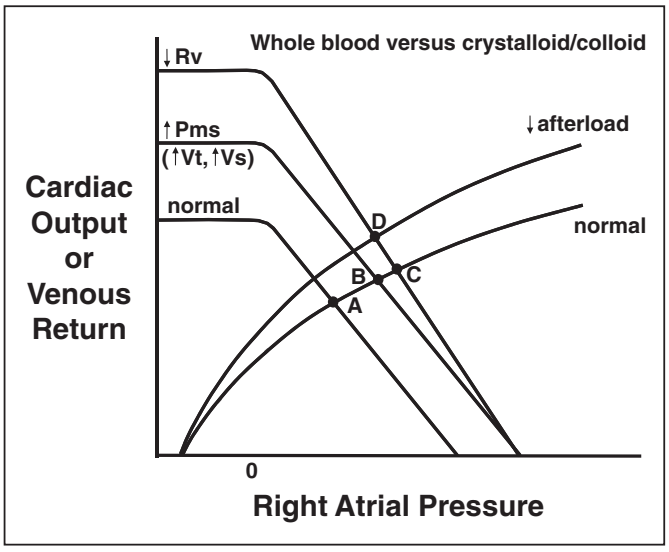

Figure 6. Effect of fluid bolus on venous return/cardiac output. P_{ms} = mean systemic pressure; Rv = venous resistance; Vs = stressed volume; Vt = total intravascular volume. See text for explanation.

effect) (30). However, RV function will deteriorate if the rise in RV afterload is acute and severe.

Because VR and CO must be identical in a closed system and both the right-heart ventricular function curve and the VR curves use P_{RA} as the independent variable, the two curves can be superimposed (**Fig. 5**), an approach first suggested by Guyton (31). The intersection of the curves will define a common VR/CO under different conditions of venous and cardiac function. A horizontal line drawn from the intersecting point of the VR and right ventricular cardiac function curves to the ordinate (y-axis) is the common value of the CO and VR. The intersection represents the common point of performance of the two interconnected systems, namely the pumping ability of the heart (dependent on preload, afterload, contractility, and heart rate) and the flow characteristics of the systemic venous circulation (dependent on Vo, Vs, Vt, C, and R_V).

Effects of Therapeutic Interventions

Although there is often an assumption that common interventions have discrete hemodynamic effects, even the simplest interventions generate several physiological responses affecting both the VR and cardiac function curves. The most common understanding of the hemodynamic effect of a fluid bolus is that it increases P_{RA} leading to an augmentation of CO through the Frank-Starling mechanism. However, this is an incomplete description and ignores the effect of the venous system. Infusion of isoviscous fluid (i.e., whole blood) increases Vt and Vs without a change in Vo resulting in an increase in P_{ms} (**Fig. 6**). The VR curve shifts parallel and to right (Fig. 6, point A to B). This causes the curve to intersect the ordinate at a higher VR/CO. For the most part, a fluid bolus increases VR by increasing P_{ms} and causing an increase in flow to the right heart, thereby taking advantage of the Frank-Starling mechanism to increase CO. However, this parallel shift in the VR curve does not fully account for the increased CO when crystalloid is infused.

Large amounts of crystalloid or colloid infusion (without red blood cells) results in transient hemodilution. Red blood cells represent a substantial component of blood viscosity. Because blood viscosity is a component of resistance for both the VR and systemic flow (arterial) equations, reduction of viscosity associated with crystalloid/colloid infusion results in a modest reduction of resistance to both venous and arterial flow. The decreased viscosity reduces R_v, so the slope of the VR curve becomes steeper (Fig. 6, point B to C). The decreased viscosity also leads to reduced pulmonary arterial afterload yielding an upward shift of the right ventricular Starling curve (Fig. 6, point C to D). Both of these effects tend to increase CO/VR. Because red blood cells account for the majority of blood viscosity, infusion of significant volumes of packed red cells will yield opposite effects. These viscosity effects are not seen with the infusion of whole blood and are usually ignored for the sake of simplicity in most analyses of VR/right heart interactions (including subsequent graphic analyses in this review).

Vasoactive compounds have even more complicated effects. Pure vasopressors such as phenylephrine and vasopressin increase R_v (decreased VR slope without a change in P_{ms}) as a consequence of vasoconstriction of large veins and the vena cava (**Fig. 7**, point A to B) (32, 33). This will tend to decrease VR. However, pure vasopressors also constrict venules and small veins and this increases the relative proportion of Vs to Vo. This will increase P_{ms} and tend to offset some of the decrease in VR (shifting the VR intercept with the abscissa [P_{ms}] to the right; Fig. 7, point B to C). Pure vasoconstrictors also usually generate an increased ventricular afterload (shifting the ventricular function curve downward; Fig. 7, point C to D). This again tends to decrease VR/CO.

If one draws a line perpendicular from the intersection of any points on the curve to the abscissa of the VR graph, the

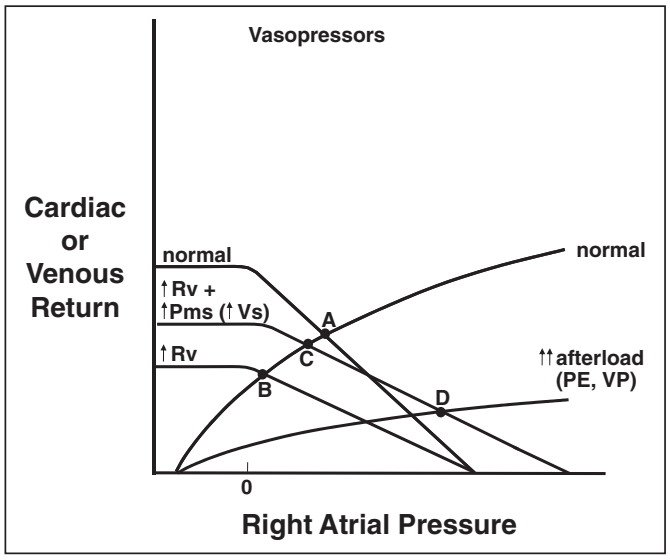

Figure 7. Effect of pure vasopressors on venous return/cardiac output. PE = phenylephrine; VP = vasopressin; P_{ms} = mean systemic pressure; Rv = venous resistance; Vs = stressed volume. See text for explanation.

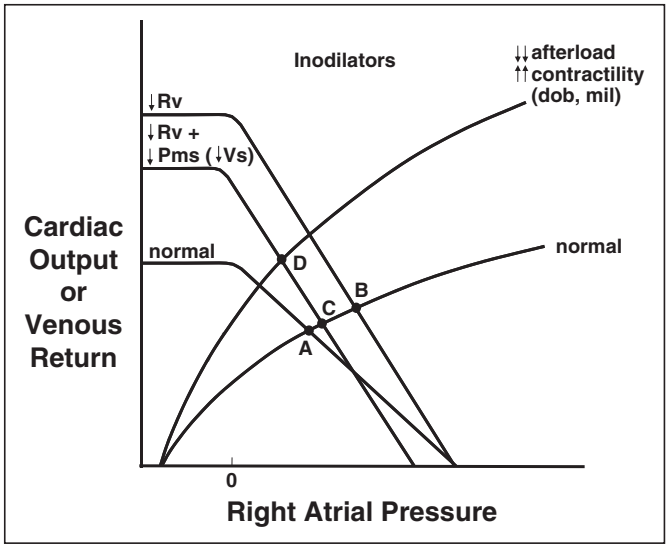

Figure 8. Effect of inodilators on venous return/cardiac output. dob = dobutamine; mil = milrinone; P_{ms} = mean systemic pressure; Rv = venous resistance; Vs = stressed volume. See text for explanation.

intersection represents P_{RA}. With the addition of a pure vasoconstrictor, the net effect (shift from point A to point D in Fig. 7) is a decrease in VR/CO but with an increase in the measured P_{RA}. This variance between estimated ventricular pressure and volumes is why static predictors of preload such as P_{RA} are inadequate in predicting CO and volume responsiveness in critically ill patients (9, 34, 35) and even in normal subjects (36). In summary, the net clinical effect of pure vasopressor administration is usually a decrease in VR/CO with an increase in P_{RA} and related filling pressures.

Inodilators like dobutamine and milrinone generate distinctly different hemodynamic effects (37, 38). The primary venous effect is venodilatation of both capacitance and resistive elements of the venous circuit. Rv falls and the slope of the VR

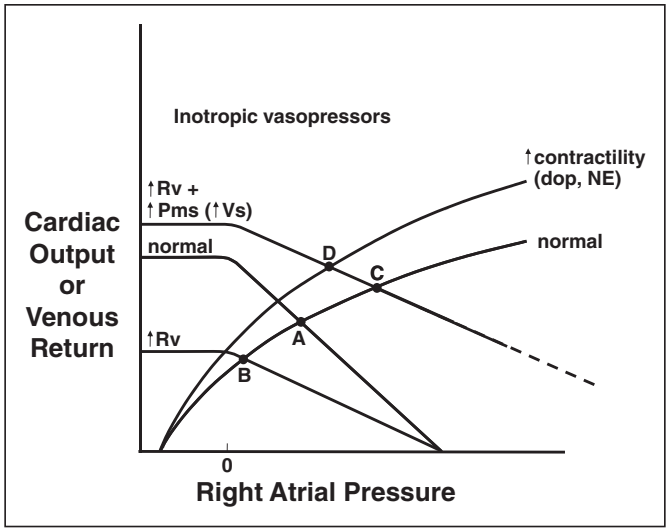

Figure 9. Effect of inotropic vasopressors on venous return/cardiac output. dop = dopamine; NE = norepinephrine; P_{ms}, = mean systemic pressure; Rv = venous resistance; Vs = stressed volume. See text for explanation.

relationship becomes steeper (**Fig. 8**, point A to B), which tends to drive up VR. However, this effect is partially offset by a decrease in the proportion of Vs to Vo, which reduces P_{ms} (Fig. 8, point B to C). The combination of arteriolar vasodilator activity and direct myocardial inotropic effect results in a marked increase in effective contractility and a shift of the ventricular function relationship upward (Fig. 8, point C to D). The effect is a substantial increase in VR/CO with a concomitant decrease in P_{RA} and related filling pressures.

Vasopressors with inotropic activity such as dopamine and norepinephrine have effects that are intermediate between pure vasopressors and inodilators. α-1 adrenergic agonist activity generates significant vasoconstriction resulting in a shallower VR response curve (**Fig. 9**, point A to B), but the capacitance beds are also constricted resulting in a shift of venous volume toward Vs, which shifts P_{ms} to the right (Fig. 9, point B to C). Because direct myocardial inotropic effects are partially offset by arteriolar vasoconstrictor effects (which increases ventricular afterload), the right ventricular cardiac function curve is not as markedly shifted as seen with the inodilator group (Fig. 9, point C to D). The net effect of a vasopressor with inotropic activity is generally to increase VR/CO, although not to the extent seen with inodilators. In addition, P_{RA} and related filling pressures are typically unchanged or modestly increased (at small to moderate drug doses).

CONCLUSIONS

The traditional teaching of cardiac physiology has focused almost exclusively on the left side of the heart. This is a consequence of the fact that much of the burden of cardiovascular diseases in advanced nations is represented by ischemic heart disease and LV failure that are well described using the most broadly accepted standard determinants of cardiovascular performance of heart rate, preload, afterload, and contractility. However, this focus ignores the critical role of the right heart

and venous system in regulating VR in states of hemodynamic compromise and shock. An approach that integrates right heart performance and VR provides a model that will be intuitively attractive to most intensivists.

In the second part of this article, we discuss the application of VR curves in the understanding and treatment of different shock states commonly encountered in critical care.

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