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 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.

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 pathophysiological 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 pathophysiological 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 I). 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
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 elec-
trical 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:

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

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 sys-
temic 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 resis-
tance (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 circula-
tion 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 sys-
temic 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 unre-
lated 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 $R_v$)
but primary dependent on any individual element. The elements contributing to cardiac function in this context
include the loads on and compliance of the right and left ven-
tricles 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 under-
stood 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 vol-
umes, and venous resistance ($R_v$). 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

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

<table>
<thead>
<tr>
<th>Structure</th>
<th>Percentage of Total Blood Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic venous system</td>
<td>64</td>
</tr>
<tr>
<td>Systemic arterial system</td>
<td>13</td>
</tr>
<tr>
<td>Capillaries</td>
<td>7</td>
</tr>
<tr>
<td>Pulmonary circuit</td>
<td>9</td>
</tr>
<tr>
<td>Heart</td>
<td>7</td>
</tr>
</tbody>
</table>

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 $P_{ms}$, which is usually understood as a measure of right ventricular pre-load (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:

$$P_{ms} = V_s/C_s$$

where $V_s$ 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 ($V_t$) 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 ($V_s$). The amount remaining in the circulation would be the unstressed volume ($V_o$).

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

$$P_{ms} = V_o/V_s$$

This equation suggests that $P_{ms}$ can be altered through two basic mechanisms: (1) a change in the total volume in the reservoir ($V_t$); or (2) a change in the proportion of $V_o$ and $V_s$ (5). Under ideal circumstances, adding or removing volume should increase and decrease $V_t$ and $V_s$, respectively, without altering $V_o$. An alteration of autonomic tone, catecholamine stress responses, or infusion of exogenous vasoactive substances will alter the ratio of $V_s$ to $V_o$ 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 1.5L) of a typical human’s total blood volume is stressed volume (6). Under normal conditions, human P\textsubscript{m} 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 \( \sim 0.187 \text{ L-mm Hg}^{-1} \) (18–22). Absent autonomic influences, infusion of 1L of fluid would therefore raise the P\textsubscript{m} by 5.3 mm Hg (1L/0.187 L-mm Hg\(^{-1}\)).

The denominator in the equation for VR, the resistance to VR or R\textsubscript{s}, is the other major concept that must be explored. The same basic determinants of resistance that apply for the SVR also apply to R\textsubscript{s}, that is, R\textsubscript{s} 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\textsubscript{s} 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\textsubscript{s}). They make a relatively small contribution to the volume of the venous reservoir. Increased autonomic tone or administration of vasoconstrictor compounds creates countervailing effects in increased stressed volume and P\textsubscript{m} 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 \( \tau \), 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 \( \tau_f \). In contrast, the skin has a large volume and slow flow, giving it a slow time constant, or \( \tau_s \). The fraction of blood distributed between these tissue beds with fast and slow time constants is called F\textsubscript{f} and F\textsubscript{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 \( \tau_f \) to \( \tau_s \) will have the effect of reducing R\textsubscript{s} 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 R\textsubscript{v}) in addition to any effects on P\textsubscript{m} (9).

Although VR is determined by P\textsubscript{m}, P\textsubscript{RA}, and R\textsubscript{s} 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\textsubscript{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\textsubscript{atm}). Normally, P\textsubscript{RA} exceeds P\textsubscript{PL}, and represents the downstream opposing pressure to flow in the numerator of the VR equation (P\textsubscript{m} – P\textsubscript{RA}). However, during inspiration, P\textsubscript{PL} becomes increasingly negative. This negative pleural (intrathoracic) pressure is transmitted to the right heart circuit. As a consequence, venous pressures and P\textsubscript{RA} may transiently fall below P\textsubscript{m}. Because the major extrathoracic veins are surrounded by body compartment pressures that normally approximate P\textsubscript{PL}, they collapse at the point where they enter the thoracic cavity and then act as Starling resisters (25, 26). Effectively, P\textsubscript{m} becomes the downstream pressure opposing venous flow in the numerator of the VR equation (P\textsubscript{m} – P\textsubscript{m}). 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\textsubscript{m} and the veins open again (because P\textsubscript{PL} is greater than P\textsubscript{m}) 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 pressure P\textsubscript{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\textsubscript{RA} (the downstream pressure) is 0 mm Hg and the gradient between P\textsubscript{m} and P\textsubscript{RA} is greatest. If P\textsubscript{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\textsubscript{RA} increases. According to the equation for VR (VR = P\textsubscript{m} – P\textsubscript{RA} / R\textsubscript{s}), VR can only be 0 when there is no pressure gradient (P\textsubscript{m} – P\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{s} (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\textsubscript{m} (and its constitutive factors Vt, Vs, and Vo) and/or resistance to VR (R\textsubscript{s}) will lead to changes in the shape and position of the VR curves.
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 $V_t$, whereas $V_o$ remains fixed or an increase in the proportion of $V_s$ relative to $V_o$. 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 $V_t$, whereas $V_o$ remains fixed or a decrease in the ratio of $V_s$ to $V_o$.

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., 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 $R_v$ 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 $R_v$) 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
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 $V_t$ and $V_s$ without a change in $V_0$ 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 $V_s$ to $V_0$. 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
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 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.

Vasopressors with inotropic activity such as dopamine and norepinephrine have effects that are intermediate between pure vasopressors and inodilators. $\alpha$-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.

REFERENCES