
Review Article

The role of the vasculature in regulating venous return and cardiac output: historical and graphical approach

Eric Jacobsohn MB CHB FRCPC,*
Robin Chorn BSc MB CHB FRCPC,†
Michael O'Connor MD*

Purpose: To review the physiology of cardiac output regulation by the peripheral vasculature. This will enable the clinician to understand and manage the complex circulatory changes in various forms of shock, and in other common altered circulatory states encountered in anaesthetic practice.

Source: Articles were obtained from a Medline review (1966 to present; search terms: shock, venous return, cardiac output) and a hand search (Index Medicus). Other sources include review articles, personal files, and textbooks.

Principal findings: At steady state, cardiac output is equal to venous return (VR). Venous return depends on mean systemic pressure (P_{MS}), which is the pressure in the peripheral vasculature driving blood flow to the heart, right atrial pressure (P_{RA}), and the resistance to venous return (R_V). When considering VR, P_{RA} is the downstream pressure to VR, and not simply an indirect measure of the volume status. The pressure gradient for VR is, therefore, $P_{MS} - P_{RA}$, and in a system obeying Ohm's Law,

$$VR = \frac{P_{MS} - P_{RA}}{R_V}$$

Shock and other altered circulatory states cause changes in both VR and cardiac function. The circulation can be conveniently described by a venous return and a cardiac output curve. By drawing these curves for each clinical situation, a clear understanding of the altered circulatory state is obtained, and treatment options can be clearly defined.

Conclusion: The peripheral circulation controls cardiac output in many clinical conditions. Manipulation of the peripheral circulation is as important to the successful treatment of shock and other altered circulatory states, as is the manipulation of cardiac output.

Objectif : Revoir la physiologie de la régulation vasculaire périphérique du débit cardiaque. Ceci devrait permettre au clinicien de comprendre et de prendre en charge les changements circulatoires complexes survenant dans les états de choc et autres états d'instabilité circulatoire rencontrés en anesthésie.

Source : Les articles ont été compilés grâce à un survol de Medline (de 1966 jusqu'à maintenant ; mots-clés : choc, retour veineux, débit cardiaque) et une recherche manuelle (Index Medicus). Des articles de revue, des dossiers personnels et des manuels ont aussi été utilisés.

Principales constatations : À l'état d'équilibre, le débit cardiaque est égal au retour veineux (RV). Le RV dépend de la pression systolique moyenne (P_{SM}) laquelle est constituée de la pression vasculaire périphériques qui amène le sang au coeur, la pression auriculaire droite (P_{AD}) et la résistance au retour veineux (R_V). Si on examine le RV, on constate que la P_{AR} est la pression d'aval du RV et non simplement une mesure indirecte de la volémie. Le gradient de la pression pour RV est donc $P_{SM} - P_{AR}$ et ce système obéit à la loi d'Ohm,

$$RV = \frac{P_{SM} - P_{AR}}{R_V}$$

Le choc et les autres états d'instabilité circulatoire modifient à la fois le RV et la fonction cardiaque. Il est commode de représenter la circulation par une courbe du retour veineux et du débit cardiaque. Le tracé de ces courbes pour chacune des situations cliniques permet de mieux comprendre l'état d'instabilité circulatoire et d'accéder à des options thérapeutiques clairement définies.

Conclusion : Dans plusieurs situations cliniques, la circulation périphérique contrôle le débit cardiaque. La manipulation de la circulation périphérique constitue un traitement important du choc et des autres états d'instabilité circulatoire au même titre que la manipulation du débit cardiaque.

From the Department of Anesthesia and Critical Care, University of Chicago, Chicago, IL* and The Department of Anesthesia, University of Southern California, Los Angeles, CA†

Address correspondence to: Dr. Eric Jacobsohn, Department of Anesthesia and Section of Critical Care Medicine, University of Manitoba, Health Sciences Centre, GH723-820 Sherbrook Street, Winnipeg, Manitoba, R3A 1R9 Canada.

Accepted for publication April 27, 1997.

PHYSIOLOGY OF VENOUS RETURN AND CARDIAC OUTPUT REGULATION

History and circulatory models

Circulatory model of Weber

Circulatory model of Starling and Bayliss

Circulatory model of Starr and Rawson

Circulatory model of Guyton

The multiple circuit circulatory model

Integration of cardiac function and venous return

VENOUS RETURN AND CARDIAC OUTPUT IN PATHOPHYSIOLOGICAL STATES

Shock

Hypovolaemic shock

Cardiogenic shock

Distributive shock

Obstructive shock

Spinal shock

Mixed

Miscellaneous

Venous return and cardiac output in other common clinical situations

Cardiopulmonary bypass

Pregnancy

The effect of volatile anaesthetic agents on circulatory function

CONCLUSION

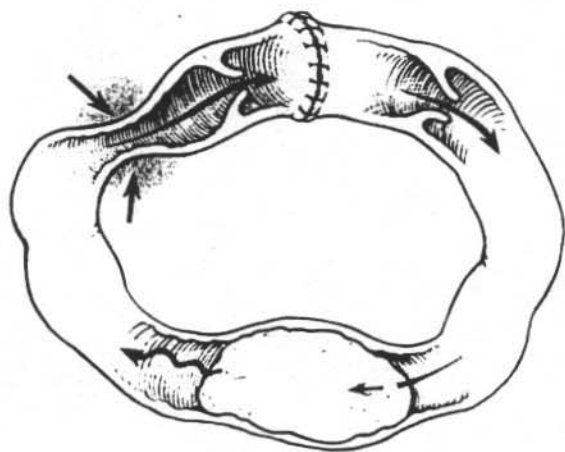


FIGURE 1 Weber's circulatory model. The cut ends of a loop of intestine are sewn together and valves fashioned to allow flow as indicated. The sponge represents the microcirculation. Pressures are measured at several points in the fluid-filled circuit, both at rest (hydrostatic mean pressure) and while being intermittently compressed (hydrokinetic mean pressure).

TRADITIONALLY, cardiac output is discussed in terms of the factors that govern cardiac function, which include preload, afterload, rate, rhythm, and contractility. While this perspective is helpful in dealing with patients whose circulatory function is limited by diseased hearts, it is incomplete. Under normal circumstances, cardiac output is controlled by the peripheral vasculature, which is as energetic at returning blood to the heart as the heart is at pumping blood to the periphery. The importance of the systemic vasculature in regulation of the cardiac output is not immediately apparent when considering the above determinants of cardiac output. However, preload is the force distending the heart at end diastole, and is dependent on the interaction of the heart and the amount of blood returning to the heart from the peripheral vasculature. This review will examine the factors that regulate venous return (VR), and the importance of VR in the control of the cardiac output in both physiologic and pathophysiologic conditions. This will enable the clinician to understand clearly and manage the haemodynamic changes in the many forms of shock and other altered circulatory states.

PHYSIOLOGY OF VENOUS RETURN AND CARDIAC OUTPUT REGULATION BY THE VASCULATURE

History and circulatory models

To understand the concept of the regulation of cardiac output by the peripheral circulation, it is important to analyse the mathematical and experimental models that have led to the current knowledge of the circulation.

Circulatory model of Weber

Much of our knowledge about the behaviour of the circulation has its origins in the work of Weber.¹ He constructed a model of the circulation by using a portion of small intestine and connecting the two cut ends (Figure 1). The pressure in the fluid-filled system was measured during a no-flow state, and was called the *hydrostatic mean pressure*. When the system was compressed and flow was present, pressures at several points around the system were measured, and the average of these pressures calculated. This was called the *hydrokinetic mean pressure*. Weber established that the hydrostatic mean pressure and the hydrokinetic mean pressure were equal. He concluded that the pump caused a reduction in pressure on the venous side and an increase on the arterial side. He established that the mean pressure in the model could only be increased by distending the tubes through the addition of more fluid. He proposed that that system mimicked the human circulation, but did not go on to explore this in humans.

Circulatory model of Starling and Bayliss

The haemodynamic importance of these findings was further studied by Bayliss and Starling in 1894.² They were embarrassed that the importance of Weber's findings in 1850 had gone unrecognized for so many years. They stated that "the experimental results that we wish to bring forward are largely such as might be predicted by anyone with a knowledge of elementary principles of the circulation. Our justification in bringing them forward, however, is that they have not been so predicted, and it was only after obtaining the results that we asked ourselves why they had not occurred to us before. In fact, they seem to be part of a forgotten or disregarded chapter in the physiology of circulation." They reasoned that, if blood were at a standstill, the pressure everywhere in the system would be equal, that is the pressure in the arteries and the veins would be at Weber's hydrostatic mean pressure. If the heart now began to pump, pressure in the arteries would increase and pressure in the veins decrease. There must be a neutral point where pressure would not change as flow commenced. They reasoned that the point at which pressure neither increased nor decreased must lie on the venous side of the capillaries.³ They noted that "what does fall from the arteries through the capillaries and back to the heart is the energy level at any point. The total energy is the sum of the hydrostatic and kinetic energies. Because of the large capillary bed, the flow is slow there and hence the kinetic energy is low, and the hydrostatic energy is high. In the veins, the kinetic energy is high and the hydrostatic pressure is low. Therefore, it follows that with the inauguration of the circulation, the point where the pressure is neither raised nor lowered must lie on the venous side of the capillaries." They went on to call this pressure *mean systemic pressure* (P_{MS}), which was synonymous with the hydrostatic mean pressure previously described by Weber. They cautioned not to confuse P_{MS}

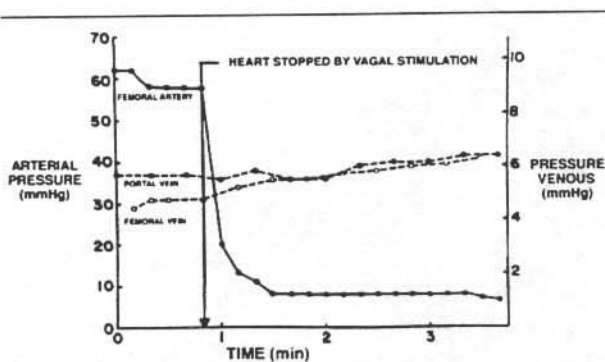


FIGURE 2 Bayliss and Starling's experiment to measure P_{MS} in a dog. When the circulation is arrested, the arterial and venous pressure equilibrate at the P_{MS} .

with the mean arterial pressure. They then measured the pressure (P_{MS}) at this neutral point in a dog model (Figure 2). The dogs were anaesthetized with morphine, and cannulae were placed in the femoral vein, femoral artery, portal vein, inferior vena cava, and aorta. The vagal nerves were exposed in the neck and the cervical spines of the dogs were severed to induce complete sympathectomy. The circulation was then arrested by vagal stimulation. There could be no reflex vasoconstriction after the arrest due to the induced sympathectomy. The experiment showed that, upon cessation of the circulation, the pressure in the femoral artery, portal vein, femoral vein, aorta and IVC equilibrated at a pressure of approximately 7 mmHG. They concluded that this was the P_{MS} in a sympathectomized dog.

Circulatory model of Starr and Rawson

The importance of these studies and P_{MS} were disregarded for another 50 yr, until 1940, when Starr and Rawson⁴ developed a mechanical model to simulate congestive heart failure (Figure 3). They hypothesized

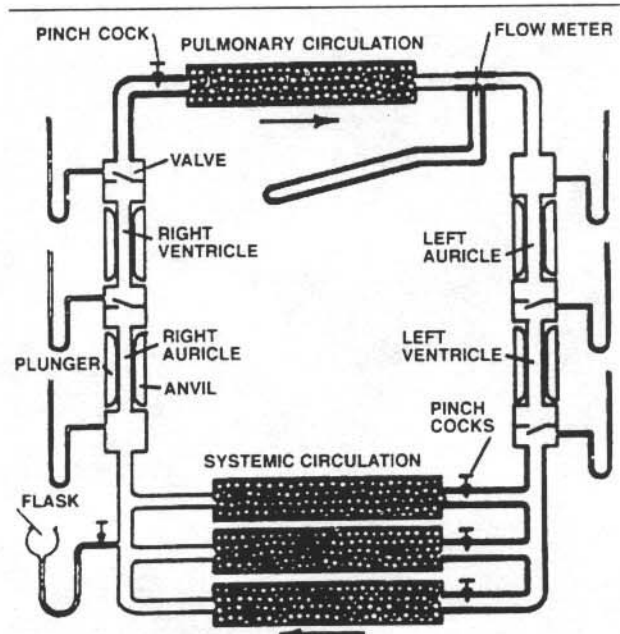


FIGURE 3 Starr and Rawson's cardiac failure model. Arterial portions, made from thick walled rubber tubing, are shown as heavy lines. Venous portions, made from flexible tubing, are shown as light lines. Capillary beds consist of tubes filled with glass beads. Manometers are connected at several points around the circuit, and a flowmeter is also present. This model could mimic many different circulatory states, including congestive heart failure. They showed that an increase in (P_{MS}) does not occur as a result of heart failure, but was a compensatory mechanism for the heart failure. (Note: Starr and Rawson renamed P_{MS} , and called it the general static pressure. However, in this review, we will call it P_{MS} to avoid confusion.)

that the P_{MS} was the *pressure driving venous return to the heart*. They postulated that P_{MS} was increased in congestive heart failure as a compensatory mechanism for decreased cardiac contractility. In their model, they could alter volumes, pressure, flows, and make the individual chambers fail. They showed that, in this mechanical model of congestive heart failure, P_{MS} was increased, not as a result of a failing heart, but as a compensatory mechanism.

They then measured P_{MS} in 64 hospitalized patients who had died from various causes.⁵ It was measured within 30 min of death by inserting a needle into the heart or a great vein. In patients dying of prolonged congestive heart failure, P_{MS} averaged 20 cm H₂O (Figure 4). In patients dying without heart failure, it averaged 10.6 cm H₂O. Because the increased pressure was present after death, they concluded that the increase in P_{MS} represented a reflex circulatory response to compensate for the poor cardiac function, and was not the result of passive congestion behind the failing heart. They postulated that this increase in P_{MS} improved cardiac output, but did not propose a mechanism. The explanation of how an increased P_{MS} improves cardiac output would come from Guyton.

Single circuit circulatory model of Guyton

When curves depicting the relationship between mean right atrial pressure (P_{RA}) and cardiac output are examined (Frank-Starling curves), it is clear that, within the normal range of cardiac function, cardiac output can vary considerably, while P_{RA} varies only slightly.

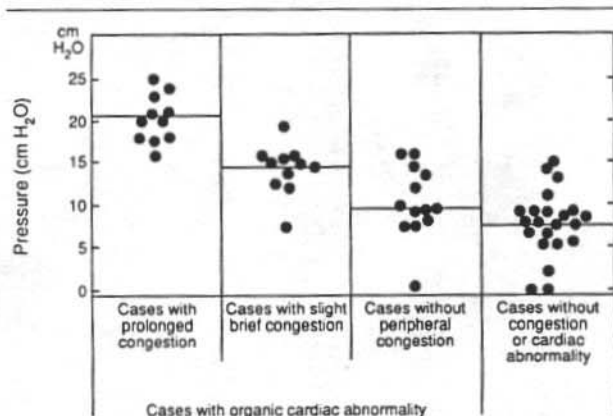


FIGURE 4 Starr and Rawson's measurement of P_{MS} in humans soon after death. The crossbars indicate average values. Mean pressure in patients with organic heart disease and prolonged congestion is higher than in patients without congestion or cardiac abnormalities. The high P_{MS} that persists after death confirms that it is a compensatory mechanism for congestive heart failure.

Therefore, it is reasonable to conclude that cardiac output is not controlled by the heart alone. Guyton^{6,7} emphasized the special importance of the peripheral circulatory factors that affect the venous return and control the cardiac output. He first developed a mathematical analysis of the circulatory system (Figure 5), and subsequently tested the analysis in well designed animal experiments. He postulated that the factors in the peripheral circulation that were important in the regulation of cardiac output were:

1) the P_{MS} ; 2) the capacitance of the veins, C ; 3) the resistance to venous return, R_v ; and 4) the peripheral distribution of blood flow.

He postulated that the P_{MS} was the *driving pressure for venous blood flow* from the periphery to the heart. Although the previous models of the circulation had defined similar pressures, the concept that the P_{MS} (or its equivalent in earlier models) was the driving force

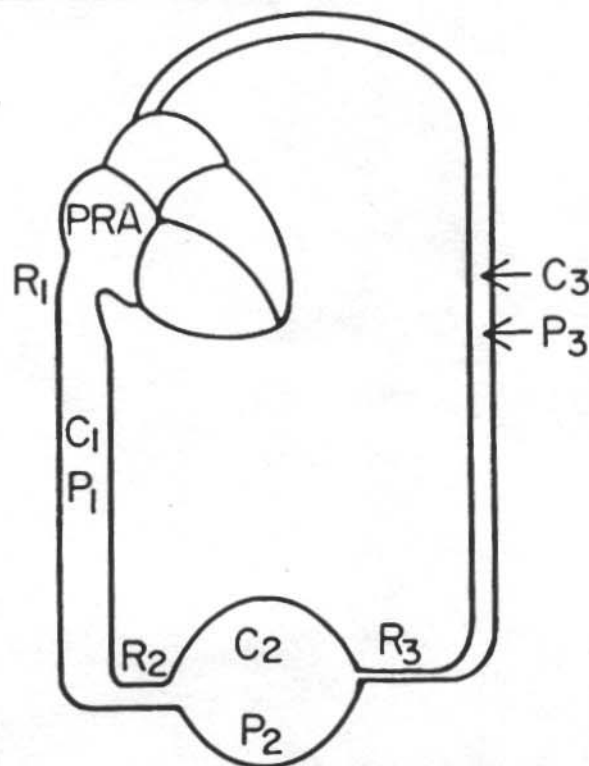


FIGURE 5 Model for Guyton's mathematical analysis of the circulation. C_3 = the capacitance of the arterial tree; P_3 = arterial pressure; R_1 = arterial and arteriolar resistance; C_2 and P_2 = capacitance and mean pressure respectively of the capillary and venular storage pool of the blood; R_2 = resistance from this venous storage pool to the major veins; C_1 and P_1 = capacitance and mean pressure of the major veins; R_1 = resistance to blood flow from the veins to the right atrium; P_{RA} = right atrial pressure; C is the capacitance of the entire circulatory system.

for blood from the periphery to the heart, had not been explored. He derived the following mathematical analysis for VR:

Equation 1

$$VR = \frac{P_{MS} - P_{RA}}{R_1 C_1 + (R_1 + R_2) C_2 + (R_1 + R_2 + R_3) C_3}$$

When the circulatory system is divided in "n" portions instead of three portions, the formula becomes:

Equation 2

$$VR = \frac{P_{MS} - P_{RA}}{R_1 C_1 + (R_1 + R_2) C_2 + \dots + (R_1 + R_2 + R_3 + \dots R_n) C_n}$$

As the value of "n" in the preceding formula approaches infinity, this formula approaches absolute validity for a system of distensible tubes.

The numerator in both these formulae is the difference between two pressures, and this may therefore be called the *pressure gradient for venous return*. It represents the difference between the pressure in the venous capacitance vessels (P_{MS}), and the P_{RA} . On the other hand, the denominator in each instance is dependent upon the resistance and capacitance of the different portions of the peripheral circulatory system. The denominator may be considered to be the resistance to venous return (R_v). The veins which primarily determine R_v include large central veins such as the venae cava, which are passively affected, and peripheral large- and medium-sized veins which can be passively affected or can be responsive to autonomic stimulation and vasoactive mediators.⁸ A general formula for this relationship can therefore be expressed as follows:

Equation 3

$$VR = \frac{\text{Pressure gradient for VR}}{R_v}$$

Guyton's single circuit model of the circulation is shown in Figure 6.⁹ The reservoir in the model represents the venous capacitance vessels, and the height of the fluid column in the reservoir represents the P_{MS} . The venous system is 40 times more compliant than the arterial circulation and is by far the biggest compartment in the peripheral circulation. The P_{MS} is determined by the volume in this compartment and by the compliance of this compartment. Because the arterial pressure generated by the heart is not transmitted to the veins, the presence or absence of flow in the system has no effect on P_{MS} . The pressure in the reservoir (P_{MS}) is, therefore, the driving pressure for

venous flow from periphery to the heart. It is easy to imagine what will happen when the pump in this model is stopped: P_{RA} will increase to P_{MS} and arterial pressure (P_a) will decrease to P_{MS} . Flow through the system does not influence the reservoir pressure (P_{MS}), that is, cardiac output has no effect on P_{MS} . An increased flow in the system can only result from an increase in the reservoir pressure (P_{MS}) or a decrease in the P_{RA} . In this model, flow from the reservoir to the pump is represented by the following equation:

Equation 4

$$\text{Flow in system (cardiac output)} = VR = \frac{P_{MS} - P_{RA}}{R_v}$$

The P_{MS} (the pressure in the reservoir) is analogous to the pressure in the circulation during a no-flow state (P_{MS}). The pressure in the reservoir is dependent on three factors: 1) the total volume of fluid in the reservoir, V ; 2) the capacitance of the reservoir, C ; and 3) the unstressed volume of the reservoir, V_0 .

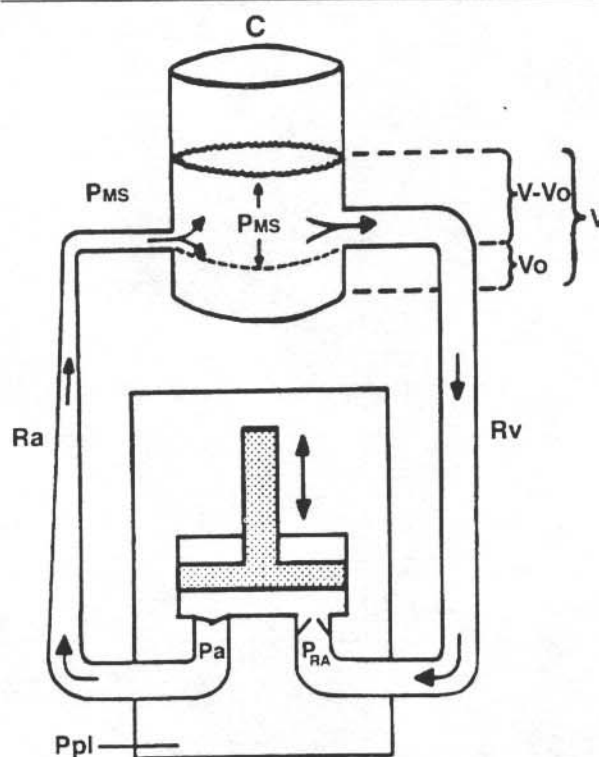


FIGURE 6 Guyton's single circuit model of the circulation. Blood from the capacitance vessels (the cylinder) flows through the R_v to the RA. Flow is proportional to the pressure gradient R_v (flow = $VR = CO = P_{MS} - P_{RA} / R_v$). V = total volume in the reservoir (capitance vessels); V_0 = the unstressed volume; R_a = the arterial resistance; R_v = the venous resistance; P_a = the mean arterial pressure; P_{PL} = pleural pressure C = capacitance of the veins.

Equation 5

$$P_{res} = P_{MS} = \frac{V - V_0}{\text{Compliance of the reservoir}}$$

1) The pressure in the reservoir can be changed by adding or subtracting volume. This would be analogous to increasing or decreasing the volume of blood in the veins.

2) The compliance of the reservoir can be measured by dividing the pressure change by the volume change. If the reservoir were a narrow cylinder (small capacitance), its compliance would be low, and the small volume change would cause a large pressure change. Conversely, if the reservoir were wide (large capacitance), its compliance would be large, and a similar change in volume would cause a much smaller change in pressure. These situations would be analogous to increasing or decreasing the capacitance of the veins by venodilation or venoconstriction.

3) The *unstressed volume* (V_0) is the volume that exists in the reservoir before there is an increase in pressure. Inclusion of the V_0 is necessary for the reservoir to mimic the vasculature, as a certain volume of blood has to be present in the veins before pressure will be exerted on the walls of the veins. Decreasing V_0 can increase the pressure in the reservoir. Hence, decreasing V_0 of the veins can maintain the P_{MS} at normal levels in the setting of a decreased intravascular volume. It is estimated that 70–80% of the blood volume in a human is unstressed. Therefore, in an average sized adult, approximately 1.5 L of blood ($30\% \times 5 \text{ L} = \text{the stressed volume}$) is the amount that actually contributes to the P_{MS} . P_{MS} has been measured to be approximately 8 mmHg in normovolaemic humans (Figure 7).¹⁰ The compliance of the human venular bed can be derived to be $0.187 \text{ L} \cdot \text{mmHg}^{-1}$ ($1.5 \text{ L} \div 8 \text{ mmHg}$). Therefore, infusing one litre of fluid acutely would increase the P_{MS} by 5.3 mmHg.

Right atrial pressures below atmospheric pressure can occur due to contraction of the respiratory muscles. To illustrate this in the model (Figure 6), the heart is surrounded by a box, representing the thorax and pleural pressure (P_{PL}). Outside the thorax, the veins are surrounded by pressure that is approximately equal to atmospheric pressure. Therefore, when a negative P_{PL} is generated by a strong respiratory effort, the negative pressure that is transmitted to the right atrium is also transmitted to the great extrathoracic veins. As the pressure in the extrathoracic veins becomes negative, the veins collapse because they are surrounded by a positive atmospheric pressure in the abdomen. When they collapse, flow is instantaneously

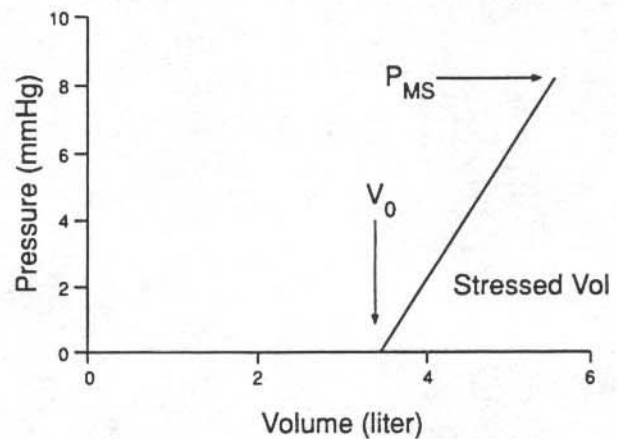


FIGURE 7 Stylized pressure-volume relationship of the human vasculature. V_0 = volume in the circulation before there is any increase in pressure. V is the total circulating volume.

and temporarily stopped; however, the intraluminal pressure in the veins immediately rises to P_{MS} . Since P_{MS} is greater than the pressure surrounding the veins, the veins open, and flow would resume. However, when the veins open and flow resumes, the negative P_{RA} would again be transmitted, and the veins would again collapse. A cyclical repetition of this process would result in a fluttering effect. The net effect is to set the pressure gradient for venous return at $P_{MS} - P_S$, where P_S is the pressure surrounding the great extrathoracic veins. If the pressure surrounding the veins is atmospheric, the maximum flow is reached at an atrial transmural pressure of zero. Therefore, VR (flow) obeys Ohm's Law when $P_{RA} \geq 0$, but the veins act as a Starling resistor when $P_{RA} < 0$.

The equation for VR is shown graphically in Figure 8. The venous return curve intercepts the abscissa at a P_{RA} equal to the P_{MS} ($VR = 0$ when $P_{RA} = P_{MS}$). The inverse of the slope of the line is the R_V . At a $P_{RA} < 0$, flow is limited by collapse of the extrathoracic veins. Guyton called the relationship between the P_{RA} and the flow *the venous return curve*. He tested the hypothesis of venous return in an animal model.⁶ Anaesthetized dogs were connected to cardiopulmonary bypass (CPB) (Figure 9). The variables that affect VR in the mathematical model were individually varied. The results (Figures 10, 11) show that: a) when other factors remain constant, VR is approximately proportional to the $P_{MS} - P_{RA}$, the pressure difference being the pressure gradient for venous return; b) the increase in the VR due to an increase in P_{MS} is not absolutely proportional to the pressure gradient, as an increase in volume is associated with decreases in

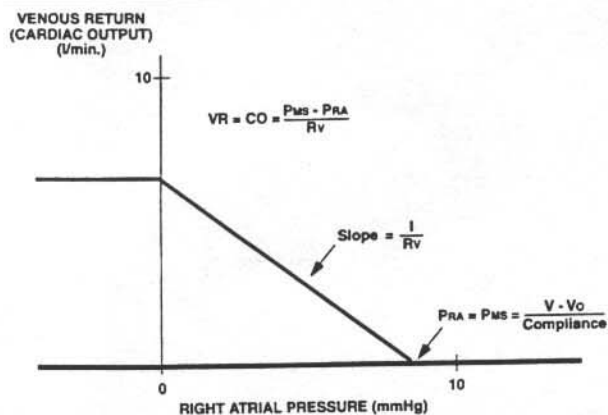


FIGURE 8 Venous return curve. Note that the P_{MS} is the point at which the graph intersects the abscissa (pressure axis). The VR reaches a maximum at a P_{RA} of 0 due to the collapsibility of the major veins. The inverse of the slope of the line is R_V .

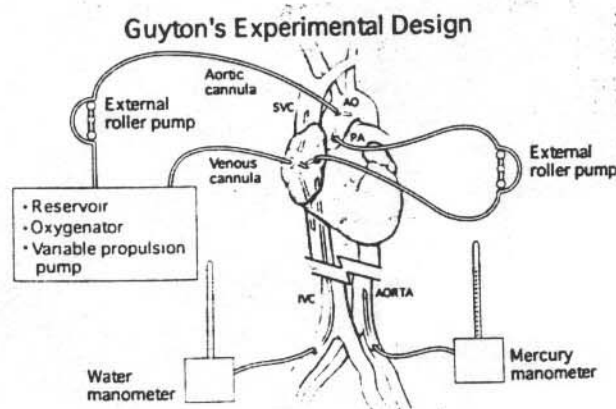


FIGURE 9 Guyton's experimental design. Blood drains to the oxygenator and is returned to the aorta by a variable propulsion pump. Manometers are placed at various points in the circulation. The external roller pump is an ancillary device to allow rapid equilibration of the venous and arterial pressures when the circulation is arrested. All the variables of VR and cardiac output can be independently varied, and the mathematical relationship can then be tested. SVC = superior vena cava; AO = aorta; PA = pulmonary artery; IVC = inferior vena cava.

the R_V (larger diameter of the veins and haemodilution); and c) the upper limit to the P_{RA} is the P_{MS} .

Figure 12 shows how changes in the P_{MS} affect VR. An increase in the total volume, a decrease in V_0 , or a decrease in the capacitance, can cause a right shift of the VR curve. Similarly, a decrease in total volume, an increase in V_0 , and an increase in the capacitance, can cause a parallel left shift of the VR curve. Changes in the R_V change the slope of the VR curve (Figure 13).

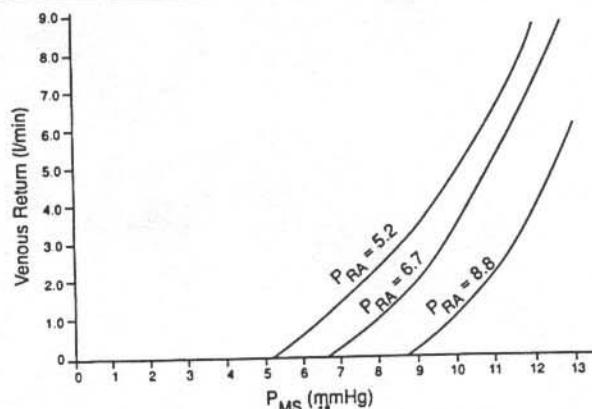


FIGURE 10 Results of Guyton's experiments. The relationship of P_{MS} and VR at different levels of P_{RA} . The graphs confirm the VR equation; flow = 0 when $P_{RA} = P_{MS}$.

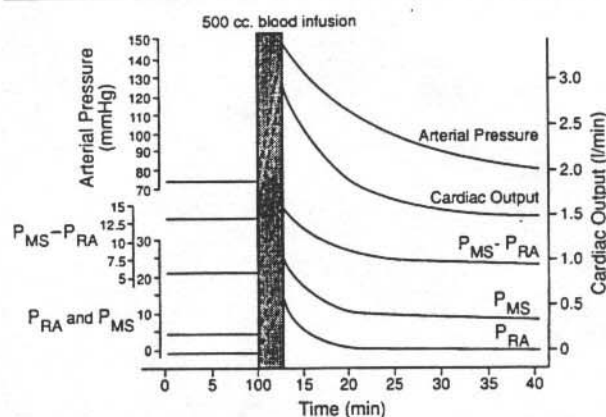


FIGURE 11 Results of Guyton's experiments. The relationship between P_{RA} , P_{MS} , cardiac output, and the arterial pressure. These graphs illustrate the parallel changes that occur in these parameters following blood infusion; arterial pressure and cardiac output increase when blood is infused. Causes of the increase in cardiac output are an increase in the gradient for VR, and a decrease in R_V (because of the increase in size of the veins and haemodilution).

Mechanisms by which R_V increase include constriction of the conducting veins, a change in the viscosity of the blood (polycythaemia), or redistribution of blood from vascular beds with fast time constants to vascular beds with slow time constants. The time constant (τ) of a vascular bed is determined by the volume of the vascular bed divided by the flow through the bed. The venous circulation is enormous and very variable. It contains venous beds such as the renal venous bed

which have low volumes and high flows, and hence fast time constants (τ_f). It also includes the venous plexus of the skin which has an enormous volume and very slow flow, and hence a slow time constant (τ_s).¹¹ The fraction of blood distributed to τ_f and τ_s is called F_f and F_s respectively. A redistribution of blood from τ_s to τ_f units will have an effect on the venous return curve similar to that of decrease in R_v . (Figure 13).

The multiple circuit circulatory model

The preceding single circuit model of the circulation does not have a pulmonary circuit or a cardiac compliance, nor does it allow for changes in the surrounding pressure on the compliant regions of the vasculature. A multiple cir-

cuit model was developed, which has a splanchnic and a non-splanchnic circuit (Figure 14).⁹ The mathematical equations derived for the multiple circuit model are complex and beyond the scope of this review. However, analysis of the multiple circuit model shows that P_{RA} has a much greater effect on VR than left atrial pressure.⁹ This is not surprising, as the systemic vasculature has a capacitance 7–10 times that of the pulmonary vasculature and, therefore, dominates physiological control of the venous circulation.¹² It is reasonable to use a single circuit model of the circulation to explain the behaviour of the circulation as a whole. For a full explanation and derivation of the multiple circuit model, readers are referred to an excellent review by Sylvester *et al.*⁹

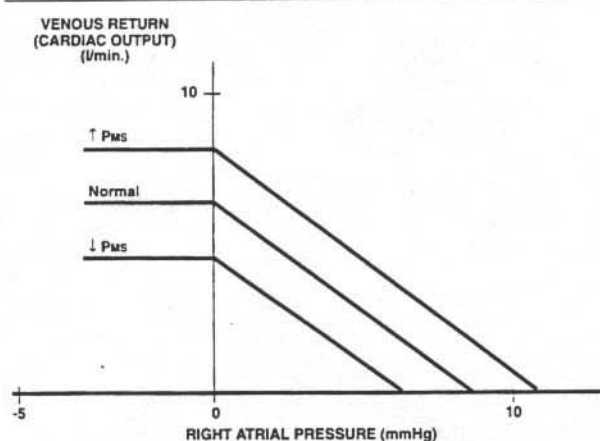


FIGURE 12 Changes in the P_{MS} . A decrease in P_{MS} moves the curve to the left, and an increase moves the curve to the right. C = venous capacitance; V = total volume of the system.

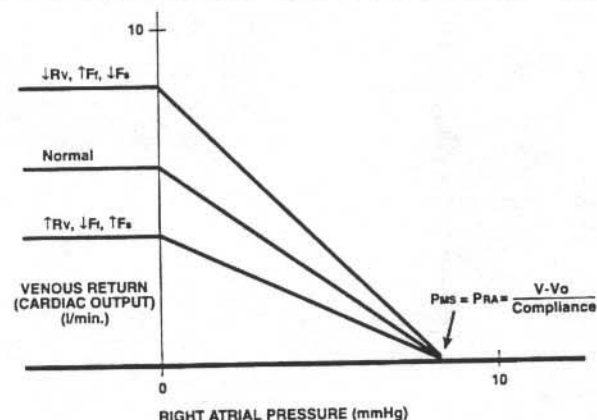


FIGURE 13 The effect of changes in the R_v and the fractional distribution of blood flow. A decrease in R_v or an increase in F_f have the effect of increasing the slope of the venous return curve. Increasing R_v and increasing F_s has the opposite effect.

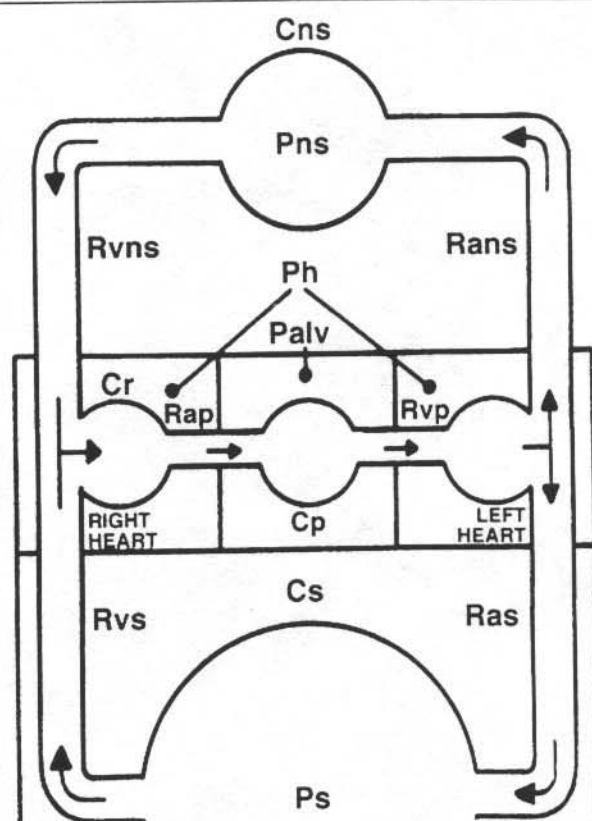


FIGURE 14 Multiple circuit model of the circulation. Blood from the splanchnic and the non-splanchnic circuit flows into the right heart (which has a compliance, C_r), from where it is then pumped into the pulmonary circuit. The pulmonary circuit has an arterial and venous resistance (R_{ap} and R_{vp}), separated by a compliance, C_p . Since most of the compliance of the pulmonary vasculature is thought to reside in alveolar vessels, the pressure surrounding C_p is the alveolar pressure, P_{alv} . From the pulmonary circuit, blood flows into the left side of the heart, which has a compliance C_L from which it is pumped into the systemic vasculature. The left and right sides of the heart are surrounded by a pressure, P_h , which can be thought of as the pressure resulting from a combination of P_{PL} and the pressure exerted by physical contact between the heart and its surrounding structures.

Cardiac function and its relationship to venous return

Cardiac function is traditionally represented by the Frank-Starling cardiac function curves, which are dependent on heart rate, contractility, and afterload (Figure 15). The intersection of the cardiac function curves and the abscissa (pressure axis) occurs at a negative value because the *transmural filling pressure* is P_{RA} relative to the pressure surrounding the heart, which is the pleural pressure (P_{PL}). In Figure 15, P_{PL} is -3 mmHg; the transmural filling pressure ($P_{RA} - P_{PL}$) is zero when P_{RA} is -3 mmHg.

One of Guyton's major contributions to the understanding of cardiac output regulation was that the venous return and cardiac function curves could be represented on the same graph (Figure 16).¹³ In a steady state, VR and cardiac output must be equal; large differences between cardiac output and VR would result in the accumulation of blood in one of the compartments and lead to the cessation of the circulation. At any time, cardiac output is determined by the *intersection* point of the VR and the cardiac function curves. The intersection represents the momentary pumping ability of the heart (rate, rhythm, contractility, afterload) and the characteristics of the circulation (V , V_O , C , R_V).

VENOUS RETURN AND CARDIAC OUTPUT IN PATHOPHYSIOLOGICAL STATES

Shock

Shock is an acute clinical syndrome initiated by hypoperfusion, resulting in organ system dysfunction.¹⁴ Hypoperfusion can result from either a) an inadequate oxygen content of the blood, b) an inadequate circu-

lation, c) failure to deliver the circulated oxygen at the cellular level, and d) failure of cells to utilize the delivered oxygen. The classification of shock has undergone many changes over the years, and continues to evolve.^{15,16,17} The summary below and Table I is a synthesis of many of these classifications, and is a practical approach to the differential diagnosis of shock.

1. Hypovolaemic shock:
 - a) Haemorrhagic:
 - 1) Observed
 - 2) Occult
 - b) Non-haemorrhagic:
 - 1) Absolute or
 - 2) Relative fluid deficit
2. Cardiogenic shock:
 - a) Myocardial (RV and/or LV)
 - b) Valvular
 - c) Conduction
 - d) Pericardial (also considered in 4)
3. Distributive shock: This describes those forms of shock that have in common vasodilatation and altered distribution of blood flow. The pathophysiology is often complex, and involves absolute or relative hypovolaemia, changes in the distribution of blood flow, and changes in cardiac function. Cardiac output may be elevated, normal or decreased, and depends on the individual clinical situation.
 - a) Septic shock
 - b) Systemic Inflammatory Response Syndrome (SIRS)
 - c) Acute adrenal insufficiency
 - d) Anaphylaxis
 - e) Thiamine deficiency (Beri-Beri)
4. Obstructive shock: This describes those forms of shock in which the major impediment is a mechanical obstruction to blood flow. This can be either:
 - a) Obstruction to venous return
 - b) Obstruction to cardiac ejection
5. Spinal shock: This is the result of either an anatomical or chemical interruption (anaesthetic) of sympathetic activity from the spinal cord. The two components of spinal shock include:
 - a) vasodilatation below the level of the spinal cord lesion
 - b) Depressed cardiac function if the lesion involves the cardiac sympathetic nerve supply (T1-T4).
6. Miscellaneous:
 - Metabolic
 - Poisons
7. Mixed: A combination of one or more of the above.

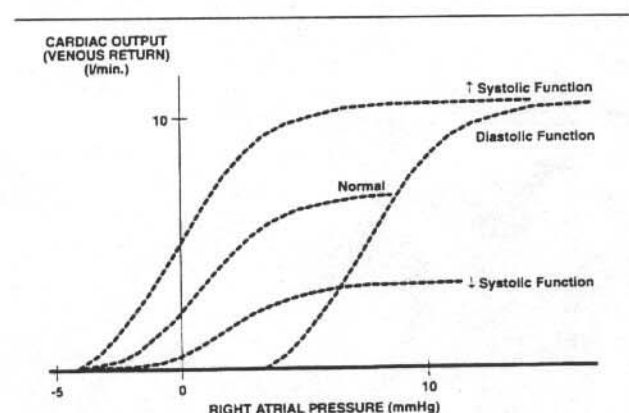


FIGURE 15 Cardiac function curves. Contractility, heart rate, rhythm and afterload determine the position of curve. The curves intersect the abscissa at negative value because the transmural pressure is zero at this pressure (see text). Note that pure diastolic dysfunction causes a parallel right-shift of the curve.

TABLE 1 Classification of shock

1. Hypovolaemic shock
 - A) Haemorrhagic:
 - Occult
 - Observed
 - B) Non-haemorrhagic
 - Absolute: fluid deficit (renal, GI, skin losses)
 - Relative: fluid redistribution (vasodilation, drugs)
2. Cardiogenic shock
 - A) Myocardial failure: (Systolic and/or diastolic; RV and/or LV)
 - 1) Ischaemia/infarction
 - 2) Myopathy: restrictive/obstructive/infiltrative/hypertrophic
 - 3) Drug induced
 - 4) Metabolic: $\downarrow\text{PO}_4^{2-}$, $\downarrow\text{Ca}^{2+}$, $\uparrow\text{H}^+$
 - 5) \uparrow afterload:
 - LV: $\uparrow\text{BP}$, HOCM, AS
 - RV: PHT, PE, HPV, PEEP, $\uparrow\text{Paw}$, ARDS, $\downarrow\text{PO}_2$, $\uparrow\text{H}^+$, $\uparrow\text{CO}_2$
 - 6) Myocardial rupture (septum or freewall)
 - 7) Myocardial contusion
 - B) Valvular
 - 1) Acute valvular insufficiency
 - a) Infectious
 - b) Traumatic
 - c) Ruptured papillary muscle
 - 2) Valvular stenosis/obstruction
 - a) Thrombus (especially prosthetic valve)
 - b) Myxoma
 - c) Infection
 - d) Stenotic valve
 - C) Conduction
 - 1) Brady- dysrhythmias
 - 2) Tachy- dysrhythmias
 - D) Pericardial Tamponade
 - Infectious, traumatic, neoplastic, metabolic, collagen vascular
3. Distributive shock
 - A) Septic
 - 1) Bacterial
 - 2) Fungal
 - 3) Viral
 - 4) Other infections
 - B) SIRS
 - 1) Burns
 - 2) Pancreatitis
 - 3) Major tissue injury
 - 4) Hepatic failure
 - C) Acute adrenal insufficiency
 - D) Anaphylaxis
 - E) Thiamin deficiency (Beri-Beri)
4. Obstructive shock
 - A) Obstruction to venous return
 - 1) Pericardial tamponade
 - 2) \uparrow Intrathoracic pressure:
 - a) Tension pneumothorax
 - b) $\uparrow\text{Paw}$
 - c) $\uparrow\text{PEEP}$
 - 3) IVC obstruction (\uparrow intraabdominal pressure)
 - a) Positioning/pressure
 - b) Tumours
 - c) Thrombus
 - d) Pregnancy
 - B) Obstruction to cardiac ejection (LV or RV)
 - 1) Massive PE (blood, tumour, air, amniotic)
 - 2) Dynamic RV or LV obstruction
 - 3) Fixed RV or LV obstruction
5. Spinal shock
 - Anatomical or anaesthetic
- A) Vasodilatation below the cord lesion
- B) Cardiac depression (lesions above T4)
6. Miscellaneous causes
 - Metabolic: thyroid storm, severe myxoedema, pheochromocytoma
 - Poisons: CO, CN and Iron
7. MIXED: Combination of above

HOCM=hypertrophic obstructive cardiomyopathy; AS=aortic stenosis; PHT=pulmonary hypertension; HPV=hypoxic pulmonary vasoconstriction; PE=pulmonary embolus; Paw=airway pressure; IVC=inferior vena cava; ARDS=adult respiratory distress syndrome.

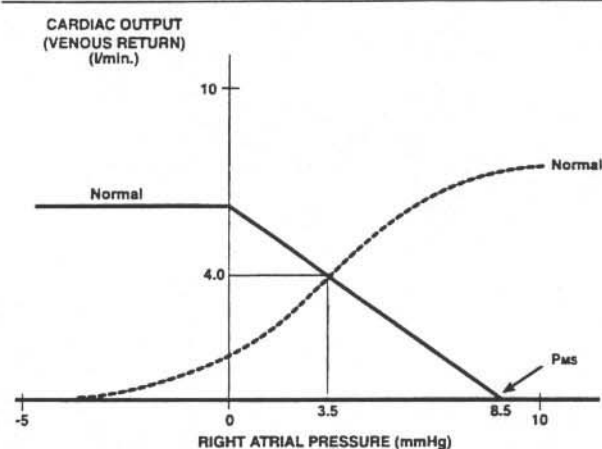


FIGURE 16 Venous return and cardiac output plotted on the same graph. At steady state, an individual has a unique VR and a unique cardiac function. The thin line shows the cardiac output and P_{RA} for this particular situation (cardiac output is 4 L·min⁻¹ at P_{RA} = 3.5 mmHg and P_{MS} = 8.5 mmHg). Cardiac output can be changed by either changing the cardiac function curve, the venous return curve, or both.

The ultimate purpose of understanding the interaction between VR and cardiac function is to be able to approach the therapy of shock and other altered circulatory states in a rational manner. Since cardiogenic and obstructive shock are principally due to cardiac function abnormalities, our therapy should be focused on optimizing pre-load, inotropy, afterload, and heart rate. On the other hand, when approaching hypovolaemic and distributive shock, our therapy is focused on abnormalities on the VR and cardiac output. Shock categories 1–5 will therefore be analysed in terms of changes in cardiac output and venous return:

Hypovolaemic shock

The pathophysiological changes associated with hypovolemia are shown in Figure 17. The compensatory mechanisms in hypovolaemic shock include an increase in intrinsic catecholamine release, which causes the cardiac function curve to move to the left, and the venous return curve to the right. There are several mechanisms that increase venous return, and these include:

1. A decrease in the capacitance of the venous reservoir due to venoconstriction. This will cause an increase in P_{MS} and will cause a right shift of the venous return curve.^{18,19}
2. A decrease in V_O . Studies by Rothe and coworkers have shown that catecholamine release shifts the blood volume from the unstressed compartment to the stressed compartment.^{20–22} This enables the patient to maintain a normal BP, car-

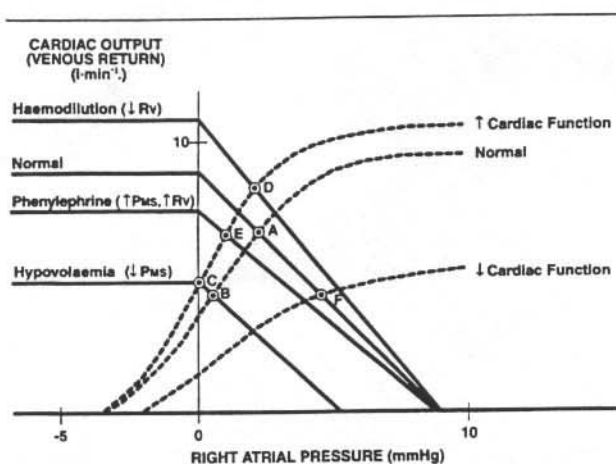


FIGURE 17 Hypovolaemic shock. A: Normal intersection of the curves. B: Acute reduction in P_{MS} . C: Left shift of the cardiac function curve due to compensatory catecholamine release. D: Resuscitation with crystalloid. The venous return curve shows a decreased R_v due to haemodilution. E: Resuscitation with phenylephrine. There is an increase in R_v because of venoconstriction. F: Refractory hypovolaemic shock. This occurs after severe, prolonged hypovolaemia, and is associated with acidosis and cardiac depression. In this situation an inotrope such as dopamine or epinephrine, may be beneficial (see text).

diac output and P_{RA} in initial stages of hypovolaemic shock, but leaves the patient with decreased reserve. Further blood loss would result in a decreased P_{MS} , P_{RA} , and cardiac output.

3. An increase in precapillary resistance or decrease in postcapillary resistance results in the movement of fluid from interstitial space into the intravascular space, increasing the P_{MS} .²³ This fluid movement also produces a drop in haematocrit; this does not occur in the early stages of haemorrhage and is more important as a long term adaptation, as in the case of slow bleeding. The effect of a decrease in haematocrit is to decrease R_v .

Treating uncomplicated hypovolaemic shock with volume moves the venous return curve towards its normal position and, therefore, restores P_{MS} , P_{RA} , and cardiac output. Pharmacological interventions, such as the administration of vasoconstrictors and inotropes, are much less effective than giving fluid.²⁴ Phenylephrine, a pure α -adrenergic agonist, also decreases V_O and increases P_{MS} . However, phenylephrine increases the R_v by causing constriction of the conducting veins. Therefore, in hypovolaemic shock, if P_{MS} was restored with a fluid infusion or with an infusion of phenylephrine, cardiac output would be higher with fluid infusion because an infusion of crystalloid would decrease the R_v , whereas the R_v is increased with phenylephrine.

What would be the effect of epinephrine in haemorrhagic shock? Activation of α -adrenergic receptors in the periphery would result in a decrease in V_O .²⁴ This would increase the P_{MS} , P_{RA} , and cardiac output. However, this assumes that the venous α -receptors were not already maximally activated by the patient's intrinsic catecholamine release. If they were already maximally stimulated, there would be little benefit from epinephrine. The net effect of epinephrine on R_v is minimal, as the α and β stimulation have opposing effects.²⁵⁻²⁷ Epinephrine would further shift the cardiac output curve upwards, and the net effect will depend on the stage of shock. In early shock, there will be minimal effect, as cardiac output is not the limiting effect, but in late hypovolaemic shock, epinephrine may be beneficial.

Cardiogenic shock (Figures 18, 19)

Cardiogenic shock can result from either myocardial dysfunction, valvular dysfunction, conduction disturbances, or pericardial pathology. Shock caused by pericardial pathology, although cardiac in aetiology, is best considered a form of obstructive shock, and will be dealt with in that section. We will use cardiogenic shock due to ischaemia as the model in this section. The effect of cardiogenic shock is shown in Figures 18 and 19. Therapeutically, clinicians have a wide variety of options for dealing with cardiogenic shock. However, in order to optimize treatment of cardiogenic shock, each intervention has to be analysed in terms of its effect on VR and cardiac function. Volume infusion has a small beneficial effect on cardiac output by improving VR. This occurs by increasing P_{MS} and moving the venous return curve to the right. However, there is a high price in terms of pulmonary oedema formation, as the patient functions at an increased filling pressure. Vasoactive drugs are the mainstay in the treatment of cardiogenic shock. Their effects on the circulation are complex, the net effect being a balance between the overall effect on the cardiac function (rate, rhythm, contractility, afterload), and their effect on the VR.

Dopamine and dobutamine are the two most commonly used inotropes in the treatment of cardiogenic shock. There are important and substantial differences between these agents in the treatment of cardiogenic shock (Table II).²⁸⁻³⁰ The differences are accounted for predominantly by the different effect on VR and afterload. At higher doses, dopamine is a β_1 , β_2 and α -agonist, but the α effects predominate (Figure 18). In this regard, the α_1 effect of dopamine are similar to administering volume, and sometimes undesirable. The β_1 effect of dopamine moves the cardiac output curve upwards, although its α effect increases afterload and decreases the beneficial effect on contractility. In

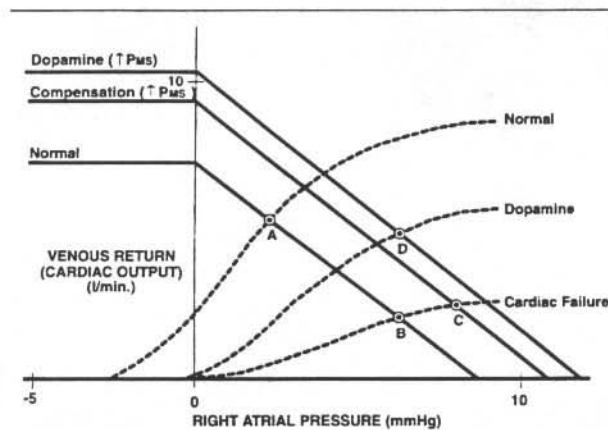


FIGURE 18 Cardiogenic shock and the effect of dopamine. A: Normal intersection of the curves. B: Depressed cardiac function. There is predominantly systolic failure, but some diastolic dysfunction is also present. Increased P_{RA} results. C: Compensation through catecholamine release. Venoconstriction moves the venous return curve to the right. The patient functions at a higher P_{MS} and P_{RA} . D: Effect of dopamine as a result of its action on cardiac function and VR (see text). Dopamine further increases P_{MS} and shifts the cardiac function curve upwards. Cardiac output increases and P_{RA} may decrease slightly. Dopamine does not change R_v due to its effect on both the α and β -adrenergic receptors.

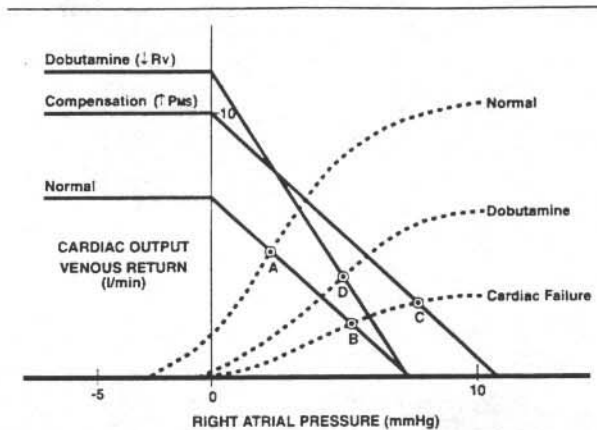


FIGURE 19 Cardiogenic shock and the effect of dobutamine. A: Normal intersection of the curves. B: Depressed cardiac function. There is mainly systolic failure, but some diastolic dysfunction is also present. Increased P_{RA} results. C: Compensation through catecholamine release. Venoconstriction moves the venous return curve to the right. The patient functions at a higher P_{MS} and P_{RA} . D: Effect of dobutamine as a result of its action on cardiac function and venous return (see text). Dobutamine increases cardiac output by improving contractility, as well as improving the VR by decreasing R_v . Unlike dopamine, P_{MS} is not increased – in fact, P_{MS} may decrease when dobutamine is started due to an unopposed β_1 effect (venodilatation). A judicious volume infusion may be required when dobutamine is initiated.

addition, the beneficial effect on cardiac output may be minimized by the tachycardia, which can reduce diastolic time and myocardial perfusion. The net effect is a result of the effect on cardiac output and VR variables, and will vary from patient to patient.

Dobutamine (Figure 19) has predominant β_1 effect, and has no α effect. This causes an increase in contractility, a decrease in afterload, and a decrease in the R_v (through venodilatation). The beneficial effects of dobutamine on contractility and afterload may, as with dopamine, be offset by an increase in heart rate and increased myocardial oxygen consumption. The decrease in R_v will be associated with increased VR and cardiac output for any combination of P_{MS} and

P_{RA} . In patients with no ability to increase contractility, dobutamine may decrease blood pressure, accompanied by a small increase in cardiac output. This may compromise vital organ perfusion. This may be offset by judicious fluid administration when dobutamine therapy is initiated.

The effect of the selective phosphodiesterase III inhibitors is similar to that of dobutamine, except that tachycardia and rate-related increased oxygen consumption and ischaemia are less.³¹ They cause an upward shift in the cardiac function curve through afterload reduction and increased contractility. In addition, they may improve diastolic dysfunction and cause a leftward shift of the cardiac function curve.³²

TABLE II Summary of the pharmacological receptor selectivity for the commonly used adrenergic drugs

Catecholamine	DA-1	β_1	β_2	α_1	α_2
Dopamine*	1-4+	0-3+	0-2+	0-3+	0-1+
Dobutamine	0	3+	1+	0-1+	0
Norepinephrine	0	2+	1+	3+	3+
Epinephrine	0	3+	3+	3+	3+
Isoproterenol	0	3+	3+	0	0

*Dopamine pharmacological effects are dose related and varies between patients. Low doses ($1-3 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) stimulate primarily the DA-1 and DA-2 receptors; high doses ($>15 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) produce predominantly α -adrenergic stimulation. 0-4 = degree of stimulation.

Phosphodiesterase III inhibitors probably decrease R_v due to intense vasodilatation.³³ As with dobutamine, they may cause severe hypotension in patients in cardiogenic shock if the overall increase in cardiac output is offset by the decrease in the afterload.

Afterload reduction is desirable in the setting of cardiogenic shock, as it allows an increase in cardiac output without the associated increase in myocardial oxygen consumption. Excessive afterload reduction is undesirable and may be hazardous. Angiotensin converting enzyme inhibitors increase cardiac output by reducing afterload and decreasing R_v .³⁴ The net effect is similar to that of dobutamine, although the increased cardiac output is due to afterload reduction increased VR.

Distributive shock

Distributive shock is a term that is used to describe those forms of shock that have in common severe vasodilatation (arterial and venous) and altered distribution of blood flow. Examples of distributive shock include septic shock,³⁵ systemic inflammatory response syndrome (SIRS), anaphylaxis,^{36–40} acute adrenal insufficiency,^{41–44} and Beri-Beri.⁴⁵ The haemodynamic pattern in distributive shock varies according to the particular clinical situation.

Using sepsis as a model for distributive shock, several clinical scenarios may occur (Figure 20). If active venodilatation is part of sepsis, R_v and P_{MS} will decrease. The net effect on VR will depend on the balance between a low R_v and P_{MS} ; a dominant decrease in R_v would increase VR, while a dominant decrease in P_{MS} would decrease VR. If venodilatation is associated with significant arteriodilatation, then cardiac output could also increase. In some cases of septic shock, contractility becomes severely depressed, either due to inherent mediators of sepsis or as a result of oxygen debt; abnormalities in cardiac function rather than VR will then determine cardiac output. This occurs particularly in the late stages of sepsis. The clinical presentation in a particular patient is related to the age of the patient, the pathogen involved, and the released vasoactive mediators. Although there is profound venodilatation in most acutely septic patients, in some cases, despite this, and in the absence of volume resuscitation, P_{MS} may remain normal.^{46,47} This may be explained by a decrease in V_O .¹⁰ The reasons why VR is usually increased in high output sepsis remains speculative. The time constant of the splanchnic vasculature may decrease, which would decrease R_v .⁴⁸ There may also be an increase in the fractional blood flow to portions of the non-splanchnic bed, which have fast time constants for venous drainage. Some

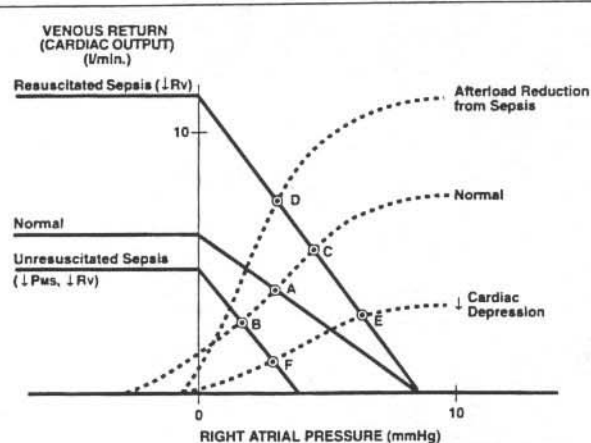


FIGURE 20 Septic shock. A: Normal intersection of the curves. B: Acute sepsis, with no fluid resuscitation. Cardiac function may be normal, but because of the severe venodilatation, the P_{MS} may be decreased. R_v is decreased. C: Volume resuscitated septic patient. P_{MS} is normal, R_v is reduced (see text), and cardiac output is increased. D: Classic high output sepsis. Profound afterload reduction (arteriodilatation) offsets any contractile depression due to the septic mediators (see text). E: Severe myocardial depression due to the septic mediators, not offset by afterload reduction (see text). Even though R_v is reduced, cardiac output is depressed. F: Profound sepsis with cardiac depression and no volume resuscitation.

studies have shown an increase in muscle blood flow in sepsis, which supports this hypothesis.^{49,50}

About 10% of patients who become septic have cardiac dysfunction, as evidenced by a normal or low cardiac output.⁵¹ Furthermore, even in those patients presenting with an elevated cardiac output, there is usually impaired contractile function, with ventricular dilatation and a reduction in the ejection fraction. However, because the heart is dilated, stroke volume changes little, and cardiac output is elevated because of an increase in heart rate. The depressed ejection fraction and ventricular dilatation are probably related to myocardial depressant factors released during sepsis.^{52,53} In addition to systolic dysfunction, some diastolic dysfunction also occurs during sepsis.^{54,55}

The therapeutic options in septic shock are partly determined by the volume status of the patient, and whether the patient has low or high cardiac output sepsis.⁵⁶ An important goal of therapy is to maintain cardiac output, tissue oxygen delivery, and perfusion pressure to vital organs. As the stressed volume is an important determinant of VR, volume resuscitation is crucial. Because of the severe vasodilatation and ongoing capillary leak, patients may require between four and eight liters of fluid to normalize P_{MS} and to

increase cardiac output. Another option is to increase P_{MS} by using norepinephrine rather than giving large volume infusions. The α -1 effect decrease V_O and increases the stressed volume.²⁴ The β_1 effects will augment myocardial function. However, the net effect on cardiac function will depend on the effect on contractility, heart rate, and the increased afterload. The effect of high dose dopamine are similar to that of norepinephrine.⁵⁷ Phenylephrine increases arterial pressure and R_v , and is therefore only useful to increase the cerebral and the coronary perfusion pressures in patients with high output sepsis. Many patients with sepsis or other causes of distributive shock progress to ARDS.^{58,59} The evolution of ARDS complicates haemodynamic management, as it makes the infusion of volume relatively unattractive.⁶⁰ Therapy with dopamine to increase P_{MS} may be preferable to volume infusions.

Obstructive shock

The pathophysiological changes in tension pneumothorax are shown in Figure 21. The cardiovascular effect of a tension pneumothorax is to limit VR by increasing the pressure in the thorax. The equation for VR becomes $P_{MS} - P_{PL}$, because P_{PL} is greater than P_{RA} (see Guyton model). Decreasing the P_{RA} below P_L will not increase VR; the VR curve will plateau at a point greater than zero. In an acute tension pneumothorax, there is an acute decrease in cardiac output, and a compensatory intense catecholamine release. This will have the effect of increasing P_{MS} . The increase in P_{PL} increases R_v by compression of the large conducting veins, but this is somewhat offset by hypoxaemia, which has been shown to decrease R_v in a dog model.^{61,62} In addition, the cardiac function curve moves down and to the right. The rightward move occurs because the transmural filling pressure is zero when P_{RA} is equal to P_{PL} , which is high. The depression of the cardiac function curve is caused by an increase in the pulmonary vascular resistance due to lung volume loss and hypoxaemia.⁶³ The only successful way to treat a tension pneumothorax is to reduce P_{PL} immediately. This is accomplished with an emergency needle thoracostomy, followed by placement of a tube thoracostomy. The use of an inotrope will not increase cardiac output, as the limitation is the VR and right shift of the cardiac function curve.

The haemodynamic changes in pericardial tamponade result from obstruction to VR, and are similar to those of a tension pneumothorax. As the pressure around the heart is increased, it becomes the limiting pressure for VR. Transmural filling pressure is zero when P_{RA} is equal to pericardial pressure. This will have

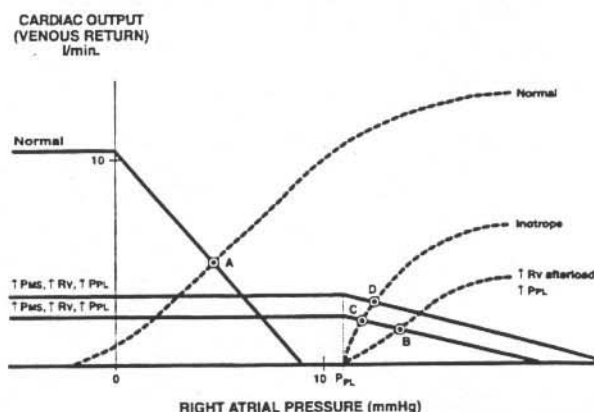


FIGURE 21 Obstructive shock due to a tension pneumothorax. A: Normal intersection of the curves. B: Tension pneumothorax. The cardiac function curve is depressed and moved to the right (see text). The R_v is increased because of compression of the conducting veins as they enter the thorax. The P_{MS} is increased because of intense catecholamine release. Venous return plateaus at P_{PL} . C: Improved contractility. The effect of an inotrope, as well as that of the intrinsic catecholamine release, does not cause an increase in cardiac output. This is due to the limitation in VR and the position/shape of the cardiac function and venous return curves. D: Volume infusion causes a slight increase in cardiac output.

a similar effect on the position of the cardiac function curve as a tension pneumothorax. The equation for venous return becomes $P_{MS} - P_{per}$, where P_{per} is pericardial pressure. Use of an inotrope to increase contractility does not lead to an increase in the cardiac output, as the VR curve is flat and the cardiac function curve is moved to the right. Definitive treatment is to decrease the P_{per} to reestablish a normal gradient for VR.

Another form of obstructive shock that is of particular importance to anaesthetists is IVC compression, as this may occur during intra-abdominal surgery and during the prone position (Figure 22). The definitive treatment is to decrease R_v by relieving the pressure on the conducting vein.

Spinal shock (Figure 23)

Spinal shock occurs as a consequence of an anatomical or pharmacological transection of the spinal cord (spinal or epidural anaesthesia).⁶⁴⁻⁶⁶ The haemodynamic consequences are determined by the level of the cord transection. The higher the transection, the greater the loss of sympathetic tone, the greater the degree of venodilatation, and the greater the decrease in P_{MS} and cardiac output. Transections above the level of T_4 cause a cardiac sympathectomy and a depressed cardiac function curve. Spinal cord lesions below T_4 are associated with normal contractility, and

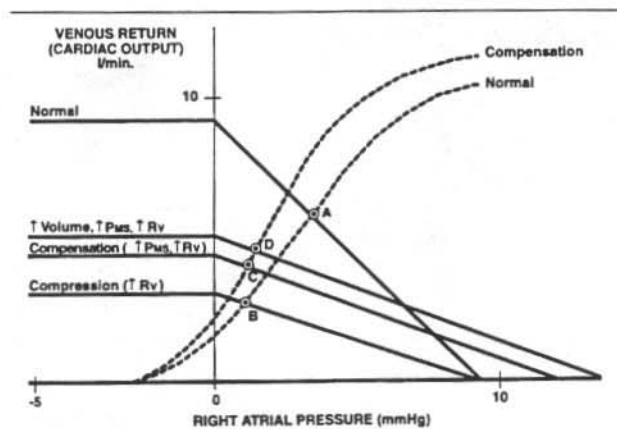


FIGURE 22 Obstructive shock due to IVC compression. A: Normal intersection of the curves. B: Increased R_v . In the acute situation, cardiac output decreases because of a decrease in VR. The increased R_v is due to direct compression of the veins and an increase in intra-abdominal pressure. C: Compensation due to catecholamine release. Intense venoconstriction increases P_{MS} , and shifts the cardiac function curve upward. However, there is only a small increase in cardiac output. D: Volume resuscitation causes a small increase in P_{MS} and cardiac output.

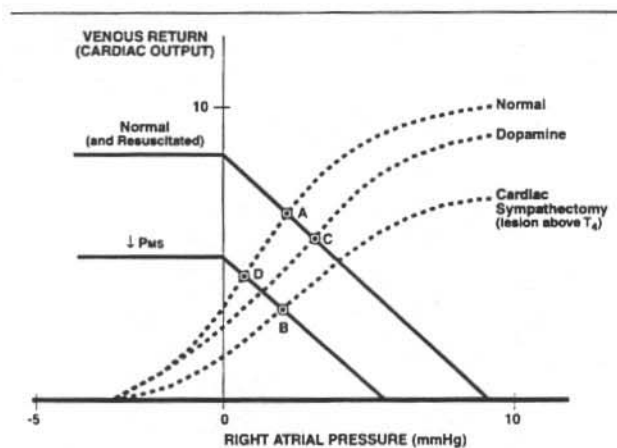


FIGURE 23 Spinal shock. A: Normal intersection of the curves. B: In a cervical cord transection or high spinal/epidural anaesthetic, the cardiac output is decreased, in part due a cardiac sympathectomy. There is also profound peripheral venodilatation due to the sympathectomy (decrease in P_{MS}). C: Treatment of a cervical cord transection with dopamine and volume resuscitation. D: Spinal cord lesion below T_4 . Cardiac function is normal. Volume infusion will increase P_{MS} and restore a normal circulation in this patient.

are treated with volume or with a vasopressor (such as phenylephrine). Using large volumes to restore the P_{MS} in these patients may be undesirable. Spinal cord transections above T_4 represent a combination of decreased contractility and decreased VR. Patients

with transections above T_4 require therapy to improve contractility and to increase the P_{MS} . Sometimes temporary pacing may be required for persistent bradycardia in high spinal cord lesions. Moderate fluid resuscitation and drugs with inotropic and peripheral vasoconstricting effects are desirable. Dopamine or norepinephrine are good choices, as they improve venous tone and improve cardiac contractility.

Other common conditions with altered circulatory states encountered in anaesthesia and critical care

Cardiopulmonary bypass (Figure 24)

Cardiopulmonary bypass (CPB) is a practical demonstration of the VR physiology.^{67,68} During CPB, the venous blood returns from the patient to the venous reservoir through siphonage. A variable propulsion pump then pumps the venous blood through an oxygenator back to the aorta. The flow from the peripheral vasculature to the right atrium is dependent on the gradient for VR, that is, $P_{MS} - P_{RA}$. During CPB, P_{RA} is determined by the flow from the right atrium to the venous reservoir. Flow from the right atrium to the reservoir occurs by siphonage, and is dependent on the size of the cannula and venous return lines, the degree of siphonage (the height between the patient and the venous reservoir), and the resistance in the lines between right atrium and the reservoir. The pressure at the tip of the cannula (P_{RA}) can therefore be decreased to a maximum of zero by allowing complete siphonage. Excess siphonage would create a negative pressure, and cause collapse of the right atrium around the cannula. P_{RA} can be increased by partially occluding the clamp on the venous return line. At a constant reservoir level, flow during CPB is therefore determined by the venous return. Flow during CPB can be increased by maximizing VR by completely opening the venous return line and thereby minimizing P_{RA} . During bypass, P_{MS} can also be altered. The volume of the venous reservoir can be transfused into the patient, increasing P_{MS} . The gradient for VR from the patient to the right atrium would therefore be increased. In addition, maximum flow can be increased by minimizing R_v .

Pregnancy

The haemodynamic changes of pregnancy are important, as aberrations can cause profound effects on uterine blood flow and fetal well being. Despite an increase in blood volume of 40% above pre-pregnant levels, the parturient at term remains susceptible to hypotension, especially during major conduction anaesthesia.^{69,70} Partial inferior vena caval and aortic occlusion by the gravid uterus is present in the majority of patients lying in the supine position

(Figure 22). This impedes VR and cardiac output by increasing R_v . Hypotension may result in some patients. In addition to hypotension, there is an increase in uterine venous pressure, further decreasing uterine blood flow. However, in most parturients, an increase in resting sympathetic tone (increase in P_{MS}) compensates for the effect of caval compression, and the blood pressure is usually maintained. However, when sympathetic tone is abolished acutely (spinal or epidural anaesthesia), an acute decrease in blood pressure may occur. If the spinal or epidural results in a high block, the cardiac sympathetics may be affected and the cardiac function curve will be depressed. This may make an already compromised situation (due to decreased VR) much worse, and profound hypotension may result. Most of these haemodynamic changes can be prevented by volume loading, proper positioning, and judicious dosing of the anaesthetic.

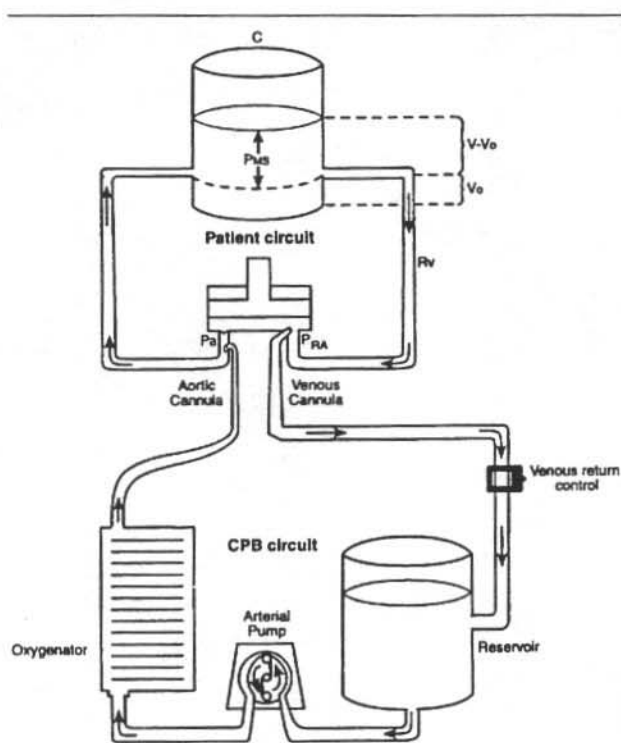


FIGURE 24 Cardiopulmonary bypass. The determinants of flow during CPB depend on patient factors (P_{MS} , P_{RA} , R_v), as well as CPB circuit factors (P_{RA} , the flow characteristics of the venous return cannula and lines, and the degree of siphonage). Some of these factors are interdependent, e.g., P_{RA} in the arrested heart is dependent on the characteristics of flow in the venous return line, and P_{MS} can be increased by transfusing the contents of the reservoir into the patient.

The effect of halothane and isoflurane on circulatory function

The effects of inhalational anaesthetics on the VR curve remain to be determined. Most studies document the effect of inhalational agents on the equilibrium point only (Figure 25).⁷¹ Volatile anaesthetics produce a dose-dependent increase in the P_{RA} , with the effect being more marked with halothane than isoflurane.⁷² Halothane causes a depression of the cardiac function curve. This is due to its direct negative inotropic effect, without compensatory increase in heart rate. Because halothane has a minimal effect on the overall systemic vascular resistance, the VR curve probably remains in a near normal position. Like halothane, isoflurane is also a direct negative inotrope, but it is also a potent vasodilator. The afterload reduction (arteriodilatation) and increased heart rate that occur with isoflurane offset the direct negative inotropic effect; the cardiac function curve is therefore depressed less than with halothane. In addition, isoflurane causes venodilatation, and this probably leads to a decrease in R_v . This will also decrease P_{MS} , but this is minimized by volume infusion prior to and during induction of anaesthesia. The decreased R_v would offset the effect on cardiac output depression. The net result is that isoflurane causes a

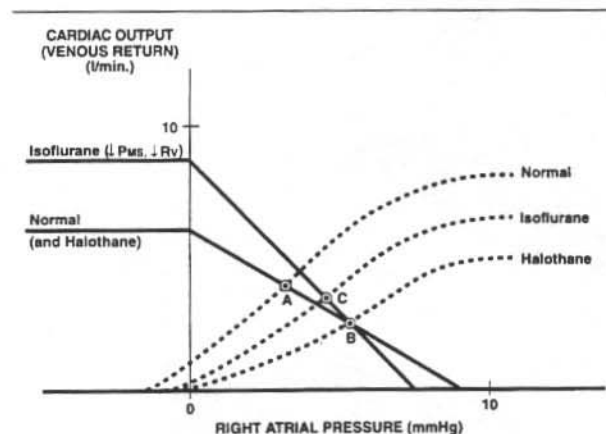


FIGURE 25 Effect of halothane and isoflurane. A: Normal intersection of the curves. B: The effect of halothane. Halothane causes a decrease in cardiac systolic function and has minimal effect on VR. There is also some diastolic dysfunction. Patients who receive halothane function at a higher P_{RA} and lower cardiac output. C: The effect of isoflurane. Patients receiving isoflurane function at a minimally reduced cardiac output, but at a higher P_{RA} . Isoflurane causes less depression of the cardiac function curve because of afterload reduction. Because it is a venodilator, it reduces R_v and P_{MS} . The reduction in P_{MS} is minimized in clinical situations by administration of volume prior to inducing anaesthesia. A small degree of diastolic dysfunction is also present.

small increase in P_{RA} , and cardiac output is only minimally depressed. With both isoflurane and halothane, there is a small right-shift of the cardiac function curve. This is because volatile agents produce varying degrees of in diastolic dysfunction.^{73,74}

Conclusion

In analyzing circulatory function, physicians focus much of their attention on the performance of the heart. This serves them well when managing patients with diseased hearts, but leaves them disadvantaged when managing patients with compromised circulations. The observation by Starling and Bayliss in 1894, that "the venous circulation was an important but disregarded chapter in the physiology of circulation,"³ still holds true today. However, by studying the concepts developed by Weber, Starling, Starr and Guyton, physicians can enhance their understanding of the circulation in many pathophysiological states, and overcome the dominance of the cardiac function in thinking about the circulation.

Acknowledgments

We wish to acknowledge Wanda Quinn for her assistance in the preparation of this manuscript.

References

- 1 Weber E. The law of pulsatile flow and its application to the circulation. Primitive model of the circulation. (German) In: *Berichte ueber die Verhandlungen der Konigl Sachsischer Cesellschaften der Wissen-Schaften zu Leipzig*, Weidmanische Buchhandlung, 1850.
- 2 Bayliss WM, Starling EH. Observations on venous pressures and their relationship to capillary pressures. *J Physiol* 1894; 16: 159–202.
- 3 Starling EH. The Arris and Gale lectures. Some points in the pathology of heart disease. *Lancet* 1897; 1: 652–5.
- 4 Starr I, Rawson AJ. Role of the "static blood pressure" in abnormal increments of venous pressure, especially in heart failure. I. Theoretical studies on an improved circulation schema whose pumps obey Starling's law of the heart. *Am J Med Sci* 1940; 199: 27–39.
- 5 Starr I. Role of the "static blood pressure" in abnormal increments of venous pressure, especially in heart failure. II. Clinical and experimental studies. *Am J Med Sci* 1940; 199: 40–55.
- 6 Guyton AC, Lindsey AW, Kaufmann BN. Effect of mean circulatory filling pressure and other peripheral circulatory factors on cardiac output. *Am J Physiol* 1955; 180: 463–8.
- 7 Guyton AC, Polizo D, Armstrong GG. Mean circulatory filling pressure measured immediately after cessation of cardiac pumping. *Am J Physiol* 1954; 179:261–7.
- 8 Bressack MA, Raffin TA. Importance of venous return, venous resistance, and mean circulatory pressure in the physiology and management of shock. *Chest* 1987; 92: 906–12.
- 9 Sylvester JT, Goldberg HS, Permutt S. The role of the vasculature in the regulation of cardiac output. *Clin Chest Med* 1983; 4: 111–26.
- 10 Magder S. Shock physiology. In: Pinsky MR, Dhainaut JF (Eds.). *Pathophysiological Foundations of Critical Care*. Baltimore, MD: William and Wilkens, 1993: 140–59.
- 11 Permutt S, Caldini P. Regulation of the cardiac output by the circuit: venous return. In: Boan J, Noordegraaf A, Raines J (Eds.). *Cardiovascular System Dynamics*. Cambridge, MA, London: MIT Press, 1978: 465–79.
- 12 Green JF. Circulatory mechanics. In: *Fundamental Cardiovascular and Pulmonary Physiology*. Philadelphia, PA: Lea and Febiger, 1982: 101–10.
- 13 Guyton A, Jones C, Coleman T. *Circulatory Physiology: Cardiac Output and its Regulation*. Philadelphia, WB Saunders, 1973.
- 14 Wally KR, Wood LD. Shock. In: Hall JB, Schmidt GA, Wood LD (Eds.). *Principles of Critical Care*. New York: McGraw-Hill, 1992: 1393–416.
- 15 Blalock A. Experimental shock. The cause of the low blood pressure produced by muscle injury. *Arch Surg* 1930; 20: 959.
- 16 Cournand A, Riley RL, Bradley SE, *et al.* Studies of the circulation in clinical shock. *Surg* 1943; 13: 964.
- 17 Weil MH, Shubin H. Proposed reclassification of shock states with special reference to distributive defects. *Adv Exp Med Biol* 1972; 23: 13–22.
- 18 Deschamps A, Magder S. Neuropeptide Y decreases splanchnic vascular capacitance. *FASEB* 1989; 3: A774.
- 19 Deschamps A, Shrier I, Magder S. Regional capacitance and unstressed volume changes in dogs during heat stress. *FASEB* 1991; 5: A1182.
- 20 Rothe CF. Reflex control of veins and vascular capacitance. *Physiol Rev* 1983; 63: 1281–342.
- 21 Rothe CF, Drees JA. Vascular capacitance and fluid shifts in dogs during prolonged hemorrhagic hypotension. *Circ Res* 1976; 38: 347–56.
- 22 Rothe CF, Johns BL, Bennett TD. Vascular capacitance of dog intestine using mean transit time of indicator. *Am J Physiol* 1978; 234: H7–13.
- 23 Lucas C, Ledgerwood A. Cardiovascular and renal response to hemorrhage and septic shock. In: Clowes G (Ed.). *Trauma Sepsis and Shock: The Physiological Basis of Therapy*. New York: Marcel Decker, 1988: 187–215.
- 24 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.

- 25 Green JF. Mechanism of action of isoproterenol on venous return. *Am J Physiol* 1977; 232: H152-6.
- 26 Peitzman AB. Hypovolemic Shock. In: Pinsky MR, Dhainaut JF (Eds.). *Pathophysiological Foundations of Critical Care*, Baltimore, MD: William and Wilkins, 1993: 161-9.
- 27 Mitzner W, Goldberg H. Effects of epinephrine on resistive and compliant properties of the canine vasculature. *J Appl Physiol* 1975; 39: 272-80.
- 28 Mutnick AH, Szymusiak-Mutnick B, Drea EJ. Dopamine versus dobutamine: are all the facts there? *Pharmacotherapy* 1990; 10: 224-9.
- 29 Rennotte MT, Reynaert M, Clerbaux Th, et al. Effects of two inotropic drugs, dopamine and dobutamine, on pulmonary gas exchange in artificially ventilated patients. *Intensive Care Med* 1989; 15: 160-5.
- 30 Francis GS, Sharma B, Hodges M. Comparative hemodynamic effects of dopamine and dobutamine in patients with acute cardiogenic circulatory collapse. *Am Heart J* 1982; 103: 995-1000.
- 31 Monrad ES, Baim DS, Smith HS, Lanoue A, Braunwald E, Grossman W. Effects of milrinone on coronary hemodynamics and myocardial energetics in patients with congestive heart failure. *Circulation* 1985; 71: 972-9.
- 32 Katz AM. Interplay between inotropic and lusitropic effects of cyclic adenosinemonophosphate on the myocardial cell. *Circulation* 1990; 82(Suppl 2): 17-11.
- 33 Lincoln TM. Cyclic GMP and mechanisms of vasodilatation. *Pharmacol Ther* 1989; 41: 479-502.
- 34 Smith TW, Braunwald E, Kelly R. Management of heart failure. In: Braunwald E. (Ed.). *Heart Disease: A Textbook of Cardiovascular Medicine*, 4th ed. Philadelphia: WB Saunders, 1992: 501-19.
- 35 Hess ML, Hastillo A, Greenfield LJ. Spectrum of cardiovascular function during gram-negative sepsis. *Prog Cardiovasc Dis* 1981; 23: 279-98.
- 36 Correa E, Mink S, Unruh H, Kepron W. Left ventricular contractility is depressed in IgE-mediated anaphylactic shock in dogs. *Am J Physiol* 1991; 260: H744-51.
- 37 Levy JH. Anaphylactic/anaphylactoid reactions during cardiac surgery. *J Clin Anesth* 1989; 1: 426-30.
- 38 Jacobsen J, Johnsen CR, Skov PS, Warberg J, Knigge U, Secher NH. Cardiovascular and hormonal responses to anaphylactic shock in the pig. *Clin Physiol* 1995; 15: 81-90.
- 39 Barsan WG, Hedges JR, Syverud SA, Dalsey WC. A hemodynamic model for anaphylactic shock. *Ann Emerg Med* 1985; 14: 834-9.
- 40 Tani H, Horibe M, Tanaka H, Arai K, Tsuchiya T. Clinical observation of hemodynamic changes during anaphylactic reaction. (Japanese) *Masui* 1991; 40: 1856-62.
- 41 Shah S, Shah A, Bhatia E, Ganjoo AK. Addisonian crisis following pericardiectomy. *Cardiovasc Surg* 1994; 2: 646-8.
- 42 Smith MG, Byrne AJ. An Addisonian crisis complicating anaesthesia. *Anaesthesia* 1981; 36: 681-4.
- 43 Parker MM, Shelhamer JH, Bacharach SL, et al. Profound but reversible myocardial depression in patients with septic shock. *Ann Intern Med* 1984; 100: 483-90.
- 44 Dorin RI, Kearns PJ. High output circulatory failure in acute adrenal insufficiency. *Crit Care Med* 1988; 16: 296-7.
- 45 Akbarian M, Yankopoulos NA, Abelmann WH. Hemodynamic studies in Beriberi heart disease. *Am J Med* 1966; 41: 197-212.
- 46 Bressack MA, Morton MS, Hortop J. Group B streptococcal sepsis in the piglet: effects of fluid therapy on venous return, organ edema, and organ blood flow. *Circ Res* 1987; 61: 659-69.
- 47 MacLean MR, Hiley CR. Effect neuropeptide Y on cardiac output, its distribution, regional blood flow and organ vascular resistances in the pithed rat. *Br J Pharmacol* 1990; 99: 340-2.
- 48 Burrell R. Human responses to bacterial endotoxin. *Circ Shock* 1994; 43: 137-53.
- 49 Matuschak GM, Martinez LH. Sepsis syndrome: pathogenesis, pathophysiology, and management. In: Pinsky MR, Dhainaut JF. (Eds.). *Pathophysiological Foundations of Critical Care*. Baltimore, MD: Williams and Wilkins, 1993: 170-86.
- 50 Van Lambalgen AA, Bronsveld W, Van den Bos GC, Thijs LG. Distribution of cardiac output, oxygen consumption and lactate production in the canine endotoxin shock. *Cardiovasc Res* 1984; 18: 195-205.
- 51 Snell RJ, Parrillo JE. Cardiovascular dysfunction in septic shock. *Chest* 1991; 99: 1000-9.
- 52 Carli A, Auclair M-C, Benassayag C, Nunez E. Evidence for an early lipid soluble cardiodepressant factor in rat serum after a sublethal dose of endotoxin. *Circ Shock* 1981; 8: 301-12.
- 53 Reilly JM, Cunnion RE, Burch-Whittman C, Parker MM, Shelhammer JH, Parrillo JE. A circulating myocardial depressant substance is associated with cardiac dysfunction and peripheral hypoperfusion (lactic acidemia) in patients with septic shock. *Chest* 1989; 95: 1072-80.
- 54 Werner HA, Herbertson MJ, Walley KR. Amrinone increases ventricular contractility and diastolic compliance in endotoxemia. *Am J Resp Crit Care Med* 1995; 152: 496-503.
- 55 Natanson C, Fink MP, Ballantyne HK, MacVittie TJ, Conklin JJ, Parrillo JE. Gram-negative bacteremia produces both severe systolic and diastolic cardiac dysfunction in a canine model that simulates human septic shock. *J Clin Invest* 1986; 78: 259-70.
- 56 Baxter F. Septic shock. *Can J Anaesth* 1997; 44: 59-72.

- 57 Stoelting RK. Sympathomimetics. In: Stoelting RK (Ed.). *Pharmacology and physiology in anesthetic practices*, 2nd ed. Philadelphia, PA: J. B. Lippincott, 1987: 264-83.
- 58 Livingston DH, Deitch EA. Multiple organ failure: a common problem in surgical intensive care unit patients. *Ann Med* 1995; 27: 13-20.
- 59 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; 20: 864-74.
- 60 Molloy DW, Ducas J, Dobson K, Girling L, Prewitt RM. Hemodynamic management of clinical acute hypoxicemic respiratory failure. Dopamine *vs* dobutamine. *Chest* 1986; 89: 636-40.
- 61 Malo J, Goldberg H, Graham R, Unruh H, Skoog C. Effect of hypoxic hypoxia on systemic vasculature. *J App Physiol* 1984; 56: 1403-10.
- 62 Sylvester J, Gilbert RD, Traystman RJ, Permutt S. Effects of hypoxia on the closing pressure of the canine systemic arterial circulation. *Circ Res* 1981; 49: 980-7.
- 63 Maughan WL, Shoukas AA, Sagawa K, Weisfeldt ML. Instantaneous pressure-volume relationship of the canine right ventricle. *Circ Res* 1979; 44: 309-15.
- 64 Tator CH. Review of experimental spinal cord injury with emphasis on the local and systemic circulatory effects. *Neuro-Chirurgie* 1991; 37: 291-302.
- 65 Bracken MB, Shepard MJ, Collins WF, *et al.* A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. *N Eng J Med* 1990; 322: 1405-11.
- 66 Bonica JJ, Berges PU, Morikawa K. Circulatory effects of peridural block: I: Effects of level of analgesia and dose of lidocaine. *Anesthesiology* 1970; 33: 619-26.
- 67 Taylor K. *Cardiopulmonary bypass. Principles and management.* Baltimore, MD: Williams and Wilkins, 1986.
- 68 Hessel E. *Cardiopulmonary bypass circuitry and cannulation.* In: Gravlee G, Davis R, Utley J (Eds.). *Cardiopulmonary Bypass. Principles and Practice.* Baltimore, MD: Williams and Wilkins, 1993.
- 69 Bromage PR. Physiology and pharmacology of epidural analgesia. *Anesthesiology* 1967; 28: 592-622.
- 70 Marx GF. Shock in the obstetric patient. *Anesthesiology* 1965; 26: 423-34.
- 71 Thomson IR. Cardiovascular physiology: VENOUS RETURN. *Can Anaesth Soc J* 1984; 31: S31-7.
- 72 Pagel PS, Kampine JP, Schmeling WT, Warltier DC. Comparison of the systemic and coronary hemodynamic actions of desflurane, isoflurane, halothane, and enflurane in the chronically instrumented dog. *Anesthesiology* 1991; 74: 539-51.
- 73 Pagel PS, Grossman W, Haering JM, Warltier DC. Left ventricular diastolic function in the normal and diseased heart. Perspectives for the anesthesiologist (2). *Anesthesiology* 1993; 79: 1104-20.
- 74 Pagel PS, Grossman W, Haering JM, Warltier DC. Left ventricular diastolic function in the normal and diseased heart. Perspectives for the anesthesiologist (1). *Anesthesiology* 1993; 79: 836-54.