Chapter 7

Blood pressure regulation

Sheldon Magder

Introduction

Regulation of arterial blood pressure is one of the most basic homeostatic processes in mammals, and the range of regulated pressures also is very similar among species. Even with a fivefold increase in cardiac output during aerobic exercise, arterial pressure in normal young males does not increase more than 50%. Regulation of blood pressure occurs over the short term, meaning seconds to minutes and over longer time periods, meaning days to months. This chapter deals primarily with acute adjustments. The analysis is based on a global view of the mechanical processes involved in regulating arterial pressure, and emphasizes changes in cardiac output and systemic vascular resistance.

What is arterial pressure?

The potential of blood vessels to be stretched by a force is determined by the elastance of the vessel, which is calculated from the change in pressure for a change in volume. The inverse of elastance is compliance. Measured arterial pressure is primarily the pressure (force per cross-sectional area) created by blood volume on the inside of elastic walls of the arteries relative to the pressure outside their walls. This pressure difference across the wall is called transmural pressure. The resulting tension in the wall can be determined from the pressures on the inside and outside of the wall and the inner and outer radii of the vessel. The analysis is often simplified by using the LaPlace relationship, which is based on the product of the transmural pressure and inner radius. However, this simplification is only valid in very thin-walled structures. Calculation of wall stress by the LaPlace relationship gives a positive value of stress, whereas the use of inner and outer radii and inner and outer absolute pressures that are not relative to atmospheric pressure gives a negative value.[1,2] The elastic force of the wall is detected by catheters with side holes and by blood pressure cuffs. Flow through a tube is determined by the difference between the inflow and outflow pressure. This drop of pressure along the length of a tube occurs because of friction from the interaction of the fluid and the inner surface of the tube as well as friction between layers that form in an ideal flowing liquid. This energy loss is called resistance and, based on the Poiseuille relationship, is calculated from the length of the tube, the fourth power of the radius, and the viscosity of the fluid as long as the flow is not turbulent.

It might seem at first that flow must always occur from an area of high pressure to an area of low pressure, but this is not true (Figure 7.1). It is the total energy loss of the system that matters and, besides the elastic pressure, there are two other forms of energy that need to be considered.[3] These are kinetic and gravitational energy. Kinetic energy is related to the product of the mass of the fluid and the square of the velocity of the fluid, which is distance per time. Velocity is related to flow, which is liter per time, by multiplying velocity by the cross-sectional area of the tube. The importance of kinetic energy becomes evident if there are variations in the cross-sectional area of a vessel. At a constant flow, the same number of particles that enter the tube must leave the tube. If a middle section of a tube has a narrowed cross-sectional area, the velocity of the particle must increase through this narrowed section so that the same number of particles to pass through (i.e., same "flow"), and thus the kinetic energy of the particles must increase. To maintain the conservation of energy, this means that elastic energy must be converted into

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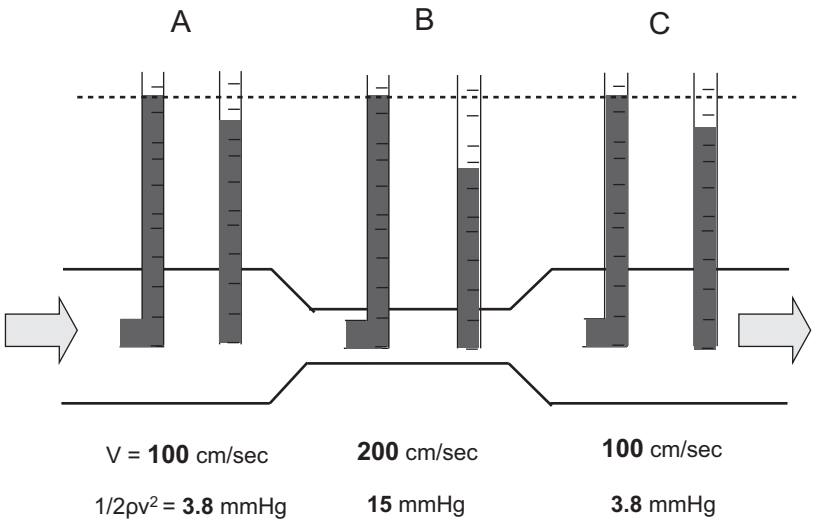


Figure 7.1. Effect of velocity on measured pressure with side-hole versus end-hole. In A the pressure measured with a side-hole is slightly lower than the pressure measured with an end-hole facing the flowing fluid. In the middle section, B, the tube is narrowed by half so that the velocity must double to allow the same flow of particles. The kinetic energy thus rises and the elastic energy decreases. In C the diameter is the same as baseline so the kinetic energy decreases and elastic energy increases again. An assumption is that there is a negligible resistive loss over this short distance.

kinetic energy. Thus elastic energy falls and kinetic energy rises. When the tube again widens, the velocity slows so that the kinetic energy is converted back into elastic energy, which means that the lateral pressure is higher downstream of the narrowed section. This has implications for the measurement of pressure. When pressure is measured with a cannula that faces the flow, the fluid that hits the cannula stops and its kinetic energy is converted into elastic energy, which means that the value measured with this device is greater than that obtained with a side-hole catheter. Kinetic energy contributes about 4 mmHg to normal arterial systolic pressure and 0.35 mmHg to the mean, but the contribution increases with increases in cardiac output and velocity, as occurs during exercise and also in sepsis. The velocity of blood flow in the vena cavae is the same as that in the aorta, so that the kinetic energy on the venous side is the same as in arteries. Since venous elastic pressure is so much lower than in arteries, the kinetic energy is a larger fraction of the total pressure. This is also true in the pulmonary circuit.

In a supine subject the third component of the energy, the gravitational component, has only a minor effect on arterial pressure measurements, but the gravitational component becomes very important in the upright posture. In a 170 cm person, the gravitational component of the pressure in the foot is almost equal to the elastic energy due to vascular volume. The gravitational component must also be considered when using fluid filled catheters to measure pressure. This is because the fluid in the device creates a gravitation force (i.e., weight) that needs to be accounted for by making sure that pressures are always measured relative to the same fixed level. This is especially important when calculating perfusion pressure in the brain or abdomen. To measure these perfusion pressures properly, the transducers for each measurement must be at the same level and not, as is sometimes suggested, with different levels for the cerebral and abdominal compartments.

Why is arterial pressure regulated at such a high value in mammals?

The right heart is able to pump the same amount of blood as the left heart through the pulmonary circulation with a mean driving pressure of only about 15 mmHg and a systolic pressure of less than 18 mmHg. So why is arterial pressure maintained in such a high range compared with the pulmonary circuit? One possibility might be to allow us to stand up. The hydrostatic gradient from the heart to the head in the upright posture of a 170 cm person is about 40 mmHg, so that the arterial pressures must be high enough to ensure steady cerebral perfusion. However, the arterial pressure of rats and mice is similar to that of humans and they obviously have no significant gravitational challenge! The answer thus is more likely related to physiological advantages. By starting with a relatively high aortic pressure, regional blood flows, such as blood flow to skeletal muscle during exercise, can be increased by lowering local resistances according to local metabolic needs without much change in aortic pressure. Thus other regions of the body do not have

to adjust their local resistances to maintain the same perfusion pressure. The alternative strategies would require that all other regions vasoconstrict to redirect flow to the working muscle, or that flow increases to all parts of the body at the same time, which would create an overwhelming demand on the heart. The value of having a constant pressure source works much like the provision of water to homes. A community's water sources are maintained at a constant pressure, often by being in a water tower. Opening taps in individual residences effectively decreases the local resistance in the places where flowing water is wanted. A second reason is that, by keeping arterial pressure relatively constant, the load on the heart remains constant. The importance of this is that pressure work requires much more energy for the heart than volume work and thus by having a relatively constant pressure the energy demands of the heart do not change very much.

What determines blood pressure?

A fundamental principle in cardiovascular physiology is that blood pressure does not determine total systemic blood flow, i.e., cardiac output, but rather that cardiac output and systemic vascular resistance determine arterial blood pressure.[4] Based on the Poiseuille relationship, arterial pressure is approximately the product of cardiac output and systemic vascular resistance. I say approximately because it should be arterial pressure minus a downstream pressure rather than simply arterial pressure, but because the downstream value is relatively constant and low, this simplification is still useful. From the clinical point of view, this simple relationship means that a decrease in arterial pressure must be because there was either a decrease in cardiac output or a decrease in systemic vasculature. Furthermore, since systemic vascular resistance is calculated, the real question for the management of hypotension becomes: did the blood pressure fall with a fall in cardiac output, in which case it is an "output" problem, or did it fall with a normal or elevated cardiac output, in which case it is a "resistance" problem. This allows the clinician to direct diagnostic reasoning to the appropriate physiological mechanism. The same rationale can be applied to the physiological processes that regulate arterial blood pressure and I will use this logic throughout this chapter. The implication is that deviations of arterial pressure from normal must be due to changes in cardiac output or to changes in systemic vascular resistance (Figure 7.2). Furthermore, regulatory mechanisms that restore arterial pressure to normal also must act through changes in cardiac output or through changes in systemic vascular resistance.

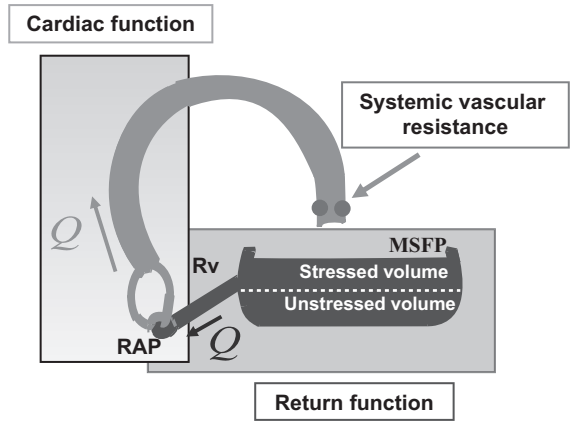
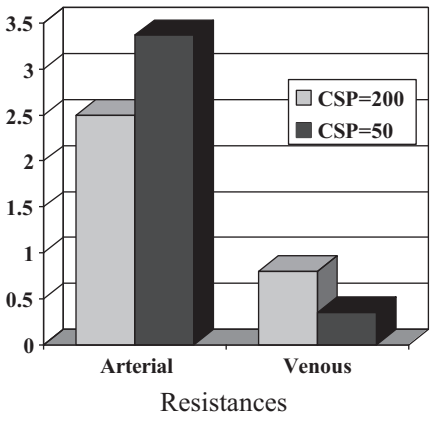


Figure 7.2. Schema for processes that can regulate blood pressure. Return function gives the determinants of venous return and are represented by a tank with an opening on the side. Stressed volume is the volume above the opening and unstressed below the opening. Stressed volume determines the elastic recoil pressure, the mean systemic filling pressure (MSFP). The tank drains through venous resistance (Rv). Cardiac function is based on the Frank–Starling relationship (Q = cardiac output). Systemic vascular resistance is regulated by arteriolar tone.

Regulation of vascular resistance

There are many factors that regulate the vascular resistance component, each of which could be a separate chapter so my comments will be limited to some broad descriptions of their roles. The factors regulating vascular resistance are easier to understand and usually more evident than the factors regulating cardiac output.

Baroreceptor regulation of arterial pressure is one of the best-studied regulatory mechanisms. These receptors are located in the carotid sinus as well as in the aortic arch but the carotid sinus receptors dominate the control. Because the carotid sinus is located outside the chest, these receptors are not directly affected by changes in pleural pressure. Their proximity to the brain also ensures that the pressure for perfusion of the cerebral vasculature is well regulated, and their location above the heart makes these receptors sensitive to the demands of being in an upright posture. A rise in blood pressure increases distention of the wall of carotid arterial baroreceptors. This increases the afferent activity of the carotid sinus nerve, which runs along with the



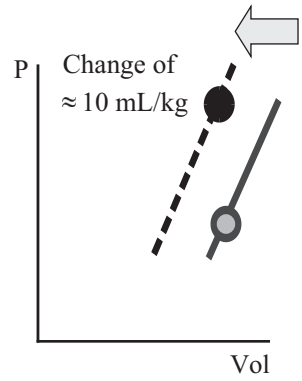


Figure 7.3. Integrated response to carotid sinus pressure (CSP). Pressure in the carotid sinus was decreased from 200 to 50 mmHg. The upper left shows the volume–pressure change in the splanchnic (Spl) region. There was a left shift of the volume–pressure relationship that recruited 10 mL of unstressed into stressed volume. The lower left bar graph indicates the change in splanchnic arterial and venous resistances with CSP hypotension. Arterial resistance increased, whereas venous resistance decreased. The right side shows the integrated response and how each factor alters venous return (VR). V0 = unstressed volume. Rv = venous resistance. Based on reference 23 (Deschamps and Magder).

glossopharyngeal (IX cranial) nerve. Centrally, this activates a vasodepressor zone, which increases vagal activity and inhibits a vasostimulatory zone, which thereby decreases sympathetic activity. The result is decreased heart rate, decreased contractility, and decreased vasoconstriction, so that there are changes in both cardiac output and systemic vascular resistance components of blood pressure.

There are central mechanisms that can result in cardiac activation and systemic vasoconstriction. During exercise, the central commands[5] that activate muscle contraction spill over into thalamic regions and increase sympathetic activity and thus produce vasoconstriction and cardiac stimulation. Neural output from the cerebral cortex such as occurs in anxious states can do the same.

There are important peripheral factors that regulate vascular resistances. Factors related to metabolic activity such as partial pressure of oxygen, oxygen saturation, potassium, osmolality, pH, and adenosine can induce vasodilatation to increase flow to match metabolic needs.[6] This process is especially active in skeletal and cardiac muscles. Vascular smooth muscle in arterioles can contract when arterial pressure is increased, or dilate when arterial pressure is decreased, and thereby maintain constant flow despite differences in arterial pressure. This is called the myogenic mechanism,[7,8] and it is especially important in coronary, cerebral, renal, and gastrointestinal vasculatures where the objective is to maintain constant flow. Increased blood flow increases shear stress on the endothelial lining of blood vessels and this induces the release of nitric oxide, which can dilate downstream resistance;[9,10] the process is called flow-mediated dilatation and acts as a feed-forward mechanism, which would cause progressive vasodilatation if not counteracted by the myogenic and metabolic regulatory mechanisms. Disease states can also affect vascular resistance. These include loss of vascular tone in sepsis or ischemia reperfusion and obstructive problems due to atherosclerotic disease.

Regulation of baseline cardiac output

Cardiac output is normally tightly related to metabolic needs.[11] For example, during aerobic exercise, cardiac output increases linearly with increasing oxygen consumption. This relationship is so tight that, if the subject's hemoglobin concentration is normal, cardiac output can be predicted within about a 5% accuracy by just knowing the oxygen consumption. Cardiac output itself is regulated by two functions: a return function, which is given by Guyton's venous return analysis and cardiac function, which is given by the Frank–Starling relationship.[4] The actual cardiac output is determined by the intersection of these two functions (Figure 7.3).

Approximately 70% of blood volume resides in small veins and venules of the systemic circulation, so that the analysis of the return function can be simplified with a reasonable approximation by just considering the drainage characteristics of the systemic veins. These create what I have called a large bathtub-like effect[12] in which the arterial inflow to this region alters the outflow not by producing an inflow pressure, but rather by increasing the volume in the region, which increases the elastic recoil in the walls of the vessels in this region. The return function then is determined by four factors: stressed volume, venous compliance, venous resistance, and the outflow pressure of the venous drainage, which is right atrial pressure (RAP).[13] Stressed volume is the volume that stretches the elastic walls of vessels, and

under basal conditions in an average-sized male stressed volume is about 1.3 to 1.4 L or approximately 30% of total blood volume. Venous compliance indicates the stretchiness of the venous reservoir and determines the slope of the relationship of stressed volume to venous pressure. This slope is essentially linear in the physiological range, and does not change acutely. Another useful term is capacitance. This refers to the total volume, which includes stressed and unstressed volume at a given pressure. Importantly, stressed volume can be increased by constriction of the walls of small veins and venules so that their unstressed volume becomes stressed volume. Venous resistance is normally only about 5% of arterial resistance but can be increased or decreased by neural input, drugs, and disease states. The high cardiac output of sepsis likely involves dilation of venous resistance vessels.

Cardiac function defines the cardiac output at different preloads considering constant heart rate, contractility, and afterload. An increase in heart rate, contractility, or decrease in afterload shift the cardiac function curve upwards, which indicates an increase in cardiac function. The preload for the heart as a whole is RAP, which should be noted is also the outflow of the return function. An increase in cardiac function allows the heart to put out the same amount at a lower RAP, which means the heart is more "permissive" in that it allows greater venous drainage.

Regulations by the system in response to changes in blood pressure

As already stated, deviations of arterial pressure from normal values must occur through either changes in cardiac output or changes in systemic vascular resistance. Changes in cardiac output must occur through changes in cardiac function or changes in the return function. It follows that regulation of deviations of arterial pressure from the normal value must involve changes in these same parameters, whether through normal physiological mechanisms or through exogenous interventions by the treating health care team.

Responses to increased arterial pressure

Increases in cardiac output or sympathetic activity are an important part of daily activities and these would increase arterial pressure unless there is reflex vasodilatation to keep arterial pressure constant. The baroreceptors play a major role in this regulation under normal physiological conditions. This is supported by the pattern of response of the carotid sinus nerve. Activity of the carotid sinus nerve occurs when distended by increases in arterial pressure and decreases when arterial pressure falls and there is less distension of the carotid sinus. A good example of the physiological need for the systemic vascular resistance to adapt to an increase in cardiac output is aerobic exercise. If there were no adjustments in systemic vascular resistance, there would be a marked rise in arterial pressure with the rise in cardiac output. The marked rise in arterial pressure would increase the afterload on the left ventricle and reduce the expected increase in cardiac output. The consequent increase in left ventricular preload would shift volume from the systemic circulation to the pulmonary circulation and reduce elastic recoil pressure for venous return from peripheral veins.[14] As already noted, during exercise, cardiac output can increase fivefold with only a 50% increase in arterial pressure and only a small increase in mean arterial pressure, which means that there is a large decrease in arterial resistance. An obvious mechanism for the fall in systemic arterial resistance is the metabolically induced vasodilatation in the working muscle, which allows the increase in muscle blood flow and ensures good matching between local blood flow and tissue needs. If there is more blood flow into the muscle, there must be more coming out, but the increase in venous return is likely not sufficient to prevent a fall in arterial pressure, and arterial pressure needs to be sustained by an increase in sympathetic tone.[15] This occurs through a number of pathways, which include afferent signals from the working muscle[16] and what is called central command,[5] which is sympathetic activation that occurs when the cerebral cortex sends motor signals to muscle tissue. If there is any decrease in arterial pressure, the baroreceptors will also contribute and provide fine tuning to the process. The set-point of the pressure range of the carotid sinus is increased during exercise, which allows systolic pressure to rise above the normal value. The increase in sympathetic activity by these mechanisms during exercise raises arterial resistance in non-working areas of the body. This helps redirect more blood to the working muscle. These responses, too, would be modified by baroreceptor feedback.

Pathological increases in arterial pressure are primarily due to an inappropriate increase in arterial resistance and failure of the appropriate vasodilatory response. A good example is essential hypertension. Since the problem is a failure of proper regulation of

arterial resistance, and considering again that blood pressure is equal to the product of cardiac output and systemic vascular resistance, the only process that could counter the inappropriate rise in vascular resistance is a decrease in cardiac output. However, cardiac output is too strongly regulated by metabolic activity to allow this to happen. Thus the system has no intrinsic mechanism to correct the problem and the only solution is the use of exogenous substances, that is, pharmacotherapy to decrease vascular resistance. These include centrally acting alpha-2 agonists, inhibition of constriction with calcium channel blockers, angiotensin converting enzyme inhibitors or angiotensin receptor antagonists, or by active dilators such as nitric oxide-releasing substances or drugs inhibiting entry of calcium into cells such as hydralazine. Arthur Guyton proposed that, in the early stages of essential hypertension, arterial pressure could be increased by expansion of vascular volume by retention of sodium with a consequent secondary increase in cardiac output. This would still require failure of normal baroreceptor activity and likely occurs to some extent during excessive salt loading, but can be resolved over a number of days by renal excretion of the excess sodium.

Responses to decreased arterial pressure

Reflex responses to decreases in arterial pressure need to occur rapidly, especially in the upright posture to protect cerebral circulation and normal brain function. The baroreceptors are thus critical for proper postural adaptations. Blood pressure is also decreased with increases in pleural pressure as can be demonstrated with a Valsalva maneuver and the accompanying baroreceptor-mediated increase in vascular resistance. In both these physiological causes of hypotension, the problem is the decrease in cardiac output.

Cardiac output can fall because of decrease in cardiac function or a decrease in return function. In these two examples the problem is the decrease in return function. In the postural stress, there is peripheral pooling of volume because of gravitational stress, and in the Valsalva maneuver the increase in pleural pressure decreases the gradient for venous return. The initial response is most likely familiar to most readers. The fall in blood pressure with the fall in cardiac output decreases distention of the carotid arterial baroreceptors. This decreases activity of the carotid sinus nerve and consequently decreases vagal tone and increases sympathetic activity. There is thus an increase in systemic arterial resistance, which helps restore blood pressure. Cardiac function, too, improves because of increased heart rate and contractility. However, an increase in cardiac function does not mean that there is restoration of cardiac output, which is the primary problem. Under normal conditions, RAP in the upright posture is at, or below, atmospheric pressure, and lowering RAP further by improving cardiac function will not increase cardiac output. This is because of what is known as the vascular waterfall effect in veins. When the pressure inside collapsible veins is less than their outside pressure, flow limitation occurs in the great veins in that lowering downstream pressure does not increase flow. When there is a vascular waterfall, cardiac output only can be increased by increasing drainage from the venous reservoir except for some other small changes. For example, increased cardiac activity can pump some volume from the thoracic compartment to the systemic circulation, but the magnitude of this is small. The primary physiological processes for increasing venous return is by the recruitment of unstressed into stressed volume by contraction of the venous capacitance vessels.[17] However, this mechanism can only work if there are reserves in unstressed volume. Decreased venous resistance could also contribute as discussed below and could help even if reserves in capacitance are low. There could also be some recruitment of volume from the interstitial space by alterations in pre- and postcapillary resistances and consequent changes in capillary filtration,[18] but this process will act over minutes to hours, whereas changes in capacitance and venous resistance are in seconds.

Two-compartment model of the systemic circulation

At this point it is necessary to add another level of complexity to the systemic circulation. The sympathetic response to hypotension as sensed by the baroreceptors does not increase arterial resistance equally in all arterial beds.[19] Resistance in non-splanchnic circulation, which is primarily muscle, increases more than the resistance in the splanchnic circulation. This increases the fraction of cardiac output going to the splanchnic circulation. From an evolutionary point of view, this makes sense for it means that more of the available blood flow can go to the more vulnerable abdominal organs. However, a shift in the fraction of flow to the splanchnic vasculature by itself will actually decrease

cardiac output. As first described by August Krogh in 1912,[20] and later by Permutt and co-workers,[21,22] when there are two parallel venous beds that have different compliances, the fractional distribution of inflow between these two regions affects the rate of return of blood to the right heart. In this model the splanchnic circulation is considered to have a large compliance, whereas non-splanchnic vasculature has a low compliance. Because of its large compliance, drainage from the splanchnic bed has a long time constant, in the range of 20 to 24 seconds, whereas that of the low compliant non-splanchnic bed has a time constant of drainage of 4 to 6 seconds. The consequence of this is that the splanchnic accumulates more of the available volume when it receives a greater fraction of the total flow, and the effective mean circulatory filling pressure (elastic recoil pressure) is reduced. This leads to a decrease in the return function.

To understand how all this could work during baroreceptor activation for hypotension, we conducted an animal experiment in which we created a right heart bypass and kept cardiac output constant with a pump.[23] We then isolated the splanchnic and limb circulations so that we could measure the regional compliance, venous resistance, unstressed volume, and flow draining each region. We isolated the carotid sinuses so that we could produce step changes in carotid sinus pressure and observe the responses in the isolated venous beds. This is called an open loop analysis of a reflex pathway because the reflex adjustments cannot feed back to baroreceptors. Lowering isolated carotid sinus pressure, the equivalent hypotension for the baroreceptors, produced a marked rise in systemic vascular resistance, but as expected increased the fraction of cardiac output going to the splanchnic bed compared with the non-splanchnic bed (Figure 7.3). However, it also resulted in recruitment of unstressed volume into stressed volume in the splanchnic bed with no significant recruitment in non-splanchnic regions. Most surprisingly, although the arterial resistance to the splanchnic bed increased, venous resistance draining this region decreased. This decreased the time constant of drainage from the splanchnic region, which increased the venous return from this region. Together, all these adaptations in an intact animal would have resulted in an increase in cardiac output of ~10%. The decrease in splanchnic venous resistance could be related to a sphincter-like mechanism in the hepatic vein, which dilates in response to beta-adrenergic agonists. On the other hand, venous resistance vessels are constricted by alpha-adrenergic agonists.

Responses to pathological causes of hypotension

Pathological causes of hypotension can be due to loss of vascular tone and decreased systemic vascular resistance, decreased cardiac output due to decreased stressed volume and decreased return function, or decreased cardiac function, or both. Loss of vascular tone is the major factor for the septic shock, for the cardiac output is usually increased. As is the case with essential hypertension, since the problem is one of a loss of vascular tone, the only defense for the body is to increase cardiac output, which is already elevated and further increases are often limited because of sepsis-induced myocardial depression and an exogenous intervention is needed. The initial step is usually an infusion of volume to increase stressed volume, and to use the Starling mechanism to increase cardiac output, but this can only work when the heart still is functioning on the ascending part of the cardiac function curve. When right heart filling is limited, pharmacotherapy is needed to correct the loss of vascular tone or to improve the cardiac response.

If hypotension is due to primary cardiac function, increasing vascular resistance will restore the pressure, but do nothing for tissue perfusion. There is thus no value for the use of pure alpha agonist such as phenylephrine, for it can only increase the load on the left heart and increase the resistance to venous return and thus tend to decrease cardiac output further.[24] Changes in preload are unlikely to be helpful because the problem is depressed cardiac function. The problem can only be resolved by improving cardiac function by an increase in contractility, decrease in afterload, or perhaps an increase in heart rate. In contrast to phenylephrine, norepinephrine can increase cardiac function and does not increase venous resistance and might even decrease it.[25] It is also crucial to determine if there is a cardiac component that can be corrected, such as an obstructed coronary artery or a malfunctioning valve.

Critical closing pressure

It is often not appreciated that there is a critical closing pressure or Starling-resistor mechanism that is active in the arterial vasculature.[26] For the whole

body this has been estimated to be around 30 mmHg,[27] but the value can be much higher in skeletal muscle, which contains a major proportion of the vasculature. The significance of this is that RAP is not the downstream pressure for the assessment of resistance in the vasculature. It also adds another control mechanism, which can significantly magnify perfusion changes when arterial resistance is low, as during exercise or in sepsis. Critical closing pressures are regulated by baroreceptor activity and sympathetic tone,[28] local metabolic factors,[26] and myogenic tone.[29] Their tone is likely lost in distributive shock with sepsis.

Starling included a critical closing pressure in his heart–lung preparation because it helped provide a constant afterload for the left ventricle, which he could then adjust and it could serve a similar role in the systemic vasculature.[30]

Distribution of resistances

So far in the discussion, systemic vascular resistance has largely been considered as one variable. However, the important factor is the distribution of resistances, for this is what determines regional flows and is why maintaining a relatively high central pressure is so useful. It needs to be appreciated that it is also not the actual value of the individual resistances, but their relative values compared with other regions as I already discussed under the fractional flow between splanchnic and non-splanchnic vascular beds. The significance of this is that, if there is someone who has an arterial pressure of 90 mmHg, but has the same proportional distribution of regional vascular resistances as someone with a systolic pressure of 120 mmHg, their regional blood flows and cardiac output could be the same, which is why people function normally with different blood pressures. However, there are some limits. One is gravitational. If systolic pressure were only 50 mmHg, the average-sized male would not be able to be sit up. Also physical limits based on the structure of vascular beds limit how low the vascular resistance can be.[31] For example, the kidney starts with a very low resistance and would not be able to decrease it adequately to allow for enough flow at pressures as low as 50 mmHg.

The implication of regional differences in vascular resistance and the variable response to sympathetic activation that I discussed under the two-compartment model is that the response to exogenous vasopressors is not completely predictable. If the vasoconstrictor does not increase cardiac output and increases all regional resistances equally, there will be no increase in blood flow to any region. Thus, an assumption when using a vasopressor is that resistance vessels in vital organs such as the brain, heart, and kidney will not constrict as much as non-essential organs, so that they can get a greater proportion of the limited cardiac output. At high doses of vasopressors, it is very likely that this is not true. The key is not to forget that pressure is not the same as flow.

Limits of the system

It should become apparent from this analysis of the regulation of arterial pressure that the physiological and therapeutic options are quite limited. If there are limited reserves in unstressed volume, sympathetic activation cannot compensate by increasing stressed volume. If the right heart is functioning on the flat part of the cardiac function curve, increasing blood volume cannot correct hypotension. If there is flow limitation to venous return because of low venous pressures, increasing cardiac function cannot increase cardiac output in response to hypotension. If there is already near maximal vasoconstriction, further sympathetic activation cannot increase vascular resistance.

Conclusions

A general approach to understanding the regulation of arterial pressure should begin by considering whether the problem and solutions involve changes in systemic vascular resistance, or changes in cardiac output, and if the problem is changes in cardiac output, is it due to changes in cardiac function or due to changes in the return function. Based on this rationale, some assessment of the status of cardiac output is key. When the primary problem is a change in cardiac output due to a change in the return function, volume status is usually the major variable to be considered. If cardiac function is the problem, choices are more limited. Drugs will be necessary to improve the function, and the cause of decreased cardiac function needs to be addressed. Finally, one must always keep in mind that blood pressure does not indicate flow.

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