

Chapter 2

Afterload

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Understanding the Concept

As discussed in Chap. 1 regarding preload, cardiac afterload is also a semi-quantitative composite assessment of a determinant of cardiac output. The four major determinants of cardiac output are cardiac preload, myocardial contractility, heart rate, and afterload. Afterload is the force against which the heart has to pump to expel blood into the vasculature. In isolated myofiber experiments, myocytes are physically loaded with defined forces in the form of a weight, to the lower end of a vertically mounted quiescent muscle sample. The opposing end of the myofiber remains tethered. The muscle is then electrically stimulated to contract and lift the additional weight. Once stimulated, the muscle develops tension, or force, until it meets and then overcomes the opposing force of the applied load, which is termed the afterload. Once the afterload is exceeded, the weight will be physically lifted and fiber shortening occurs. The degree and velocity of myofiber shortening is inversely related to the afterload applied. If both ends of the muscle sample are tethered and immobilized, or if the afterload applied is in excess of the myofiber's maximal force generation, the resulting contraction will remain isometric, meaning that the fiber length will be unchanged when tension is generated during contraction [1].

An alternate expression of the afterload is as a “stress” (defined as unit force per crosssectional area) enabling comparison of differently sized samples of myofiber. It also permits transfer of the concept to the intact ventricle. Afterload in the whole heart can be understood as the stress encountered by left ventricular myofibers as they contract against the end-diastolic volume. Ventricular wall

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forces are difficult to directly measure, but the wall tension can be described by LaPlace's equation through $\sigma = PR/2w$, where σ is wall stress, P is pressure, R is ventricular radius and w is wall thickness. More complex mathematical calculations that take into account chamber geometry can also be used to quantify end-systolic wall stress. It can be seen from the law of LaPlace that a dilated heart, with a greater radius, will have to develop a greater inward force than a smaller heart to generate the same systolic pressure.

Another concept for defining afterload is in terms of the impedance to blood flow entering the aorta, known as arterial input impedance. This parameter quantifies the ratio of change in pressure to change in flow. It can be calculated using values for arterial pressure, elasticity, vessel dimension, and blood viscosity, and requires invasive instantaneous aortic pressure and flow measurements which render it a research tool only. With the two principal determinants of ventricular afterload being systolic pressure and ventricular radius, and because the ventricular dimensions are assumed to remain relatively consistent, the systolic arterial pressure is the parameter most commonly used as a surrogate for afterload in clinical practice. In the absence of aortic or pulmonic stenosis, the maximum systolic pressure beyond the valve reflects the maximum pressure generated by the corresponding ventricle. Hence the peak aortic pressure and peak pulmonary pressure can be measured to reflect the left and right ventricular afterloads, respectively.

An inverse relationship exists between stroke volume and the afterload [2]. As above, this is a consequence of the fact that muscle cannot shorten in excess of the length determined by the total load acting upon it. When this load is increased, sarcomere shortening will stop at a greater length, and so the extent of thick-thin filament overlap and cross-bridge formation will be diminished compared to a lower afterload (Fig. 2.1).

Afterload Physiology and Theory

Afterload and Arterial Vasculature

The forces that oppose ventricular shortening are a summation of factors encountered throughout the arterial tree and can be referred to as arterial impedance. The total systolic load includes not only the impedance to flow from the large arteries, but also the impedance provided by the medium peripheral arteries and smaller arterioles. Hales suggested a simplistic model for the function of the arterial system, with the functions of cushion, conduit, and resistance being fulfilled by the proximal elastic arteries, medium-sized muscular arteries, and peripheral arterioles, respectively [3]. This classic model is useful in defining the differing properties of vessels along the arterial tree and in highlighting the peripheral arterioles as the site of the majority of peripheral resistance.

The three major determinants of arterial impedance are resistance, inertia, and compliance. Resistance in a vessel is described by the Poiseuille equation $R = 8 \times \eta \times l / \pi r^4$, where R is resistance, η represents the viscosity of blood, l is vessel

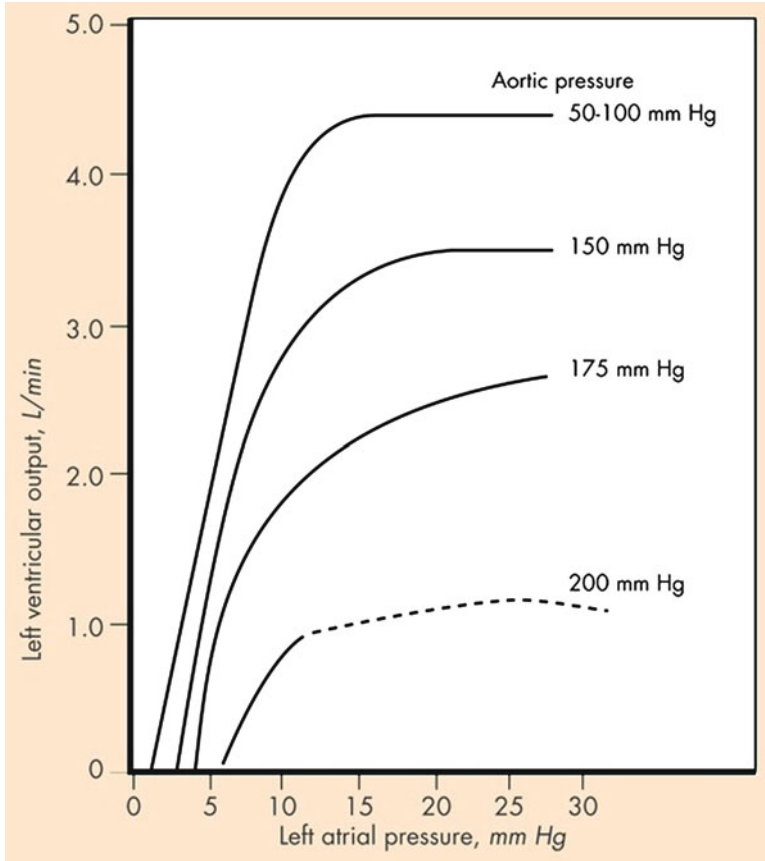


Fig. 2.1 The inverse relationship between afterload and cardiac performance. Sagawa K. Analysis of the ventricular pumping capacity as function of input and output pressure loads (Adapted from Sagawa K. Analysis of the ventricular pumping capacity as function of input and output pressure loads. In: Reeve EB, Guyton AC, editors. *Physical Bases of Circulatory Transport: Regulation and Exchange*. Philadelphia: WB Saunders; 1967; 141–149)

length, and r is vessel radius. Thus it can be seen that elevated viscosity, such as in polycythemia, will increase resistance to flow. Importantly, resistance is inversely proportional to the fourth power of the radius, enabling small changes in arteriolar diameter to have profound changes on total peripheral resistance [4]. Total peripheral resistance can be expressed with regard to the ascending aorta as $R = P_o / CO$ where P_o represents the mean arterial pressure, CO is the cardiac output, and R is the total peripheral vascular resistance. This can be re-arranged to $P_o = (CO)R = (SV)(HR)R$ by inputting the equation for cardiac output. This expression allows appreciation that the mean aortic pressure is directly related to both the cardiac output and the peripheral resistance. Inertia, which is related to the mass of the blood column, opposes acceleration of blood flow and is dependent upon the heart rate. Compliance is a property of the vascular walls, with highly compliant vessels being more distensible.

Elastance is the reciprocal of compliance. Compliance is also heart rate dependent; the rate dependence of both inertia and compliance leads to phase shifts between instantaneous pressure and flow within the pulsatile arterial system [1]. The arterial pulse waveform begins with the upstroke imposed by ventricular systole, with a rapid increase in aortic pressure in early systole. The peak proximal aortic flow velocity slightly precedes the peak pressure. The aorta and large arteries expand during systole to accommodate some of the pressure fluctuation. This intermittent input into the proximal system is translated to an almost constant flow into the distal capillary bed, fulfilling the “cushion” function of the Hales model. This is achieved by absorption of stroke volume by the large elastic vessels, with conversion of the energy of systole into stretch of the arterial walls. The walls recoil as pressure within the vessel falls, and the stored energy is returned during diastole to maintain the blood pressure and distal blood flow during this period of the cardiac cycle. This is termed the “Windkessel effect” and is dependent both upon the capacitance of the aorta and large arteries, and the resistance to flow in the smaller vessels that do not show systolic expansion.

Reflected Pressure Waves

An additional potential contributor to the afterload, not accounted for in the Hales model, is the phenomenon of retrogradely reflected pressure waves traveling from the periphery back toward the ventricle. The speed of propagation, known as the pulse wave velocity, is high enough for the reflected wave to arrive in the proximal aorta within the same cardiac cycle and so the reflection overlays the incident wave with both contributing to the arterial waveform. A reflected wave occurring during systole will increase the afterload; a reflected wave arriving in the proximal aorta during diastole is more advantageous as it will augment coronary blood flow. Major sites of reflection are arterial branch points, particularly the renal artery branches off the abdominal aorta, and the iliac bifurcation. The degree of wave reflection can change the pressure and flow waveforms seen in older subjects and in hypertensive individuals. Aging is accompanied by rises in systolic pressure and decreased arterial compliance; diastolic pressures tend to fall slightly. Medial degeneration occurs, which causes progressive stiffening of the aging larger elastic arteries, resulting in elevation of aortic systolic and pulse pressures due to a combination of a rise in the forward incident wave and early return of the reflected wave [5] (Fig. 2.2).

A Framingham sub-study documented the increases in arterial stiffness (“elastance”) with advancing age [6]. The result is increased velocity of both the incident and retrograde reflection waves, with an increase in systolic and pulse pressures. The enhanced incident wave raises myocardial oxygen demand, which can induce ventricular hypertrophy over time. In addition, the early return of reflected pressure waves adds to the afterload by augmenting late systolic pressure and removes the diastolic support of coronary blood flow; hence the favorable ventriculo-arterial coupling is progressively lost [7]. Studies have confirmed

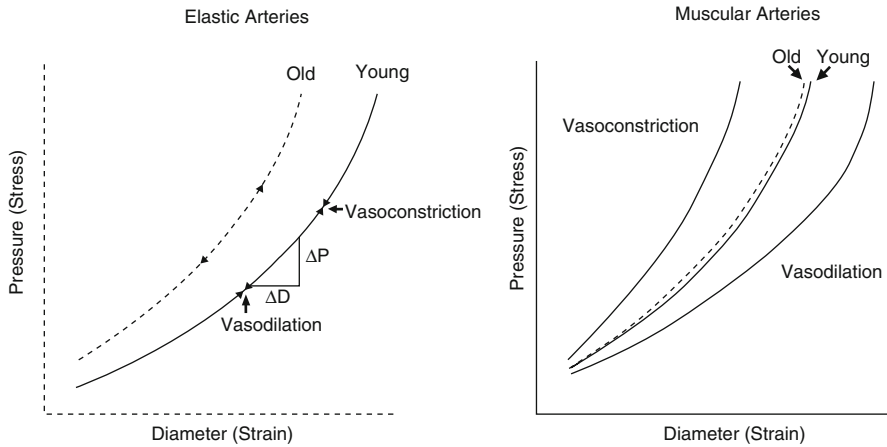


Fig. 2.2 Pressure-diameter relations for elastic and muscular arteries (From Nichols WW, Edwards DG. Arterial elastance and wave reflection augmentation of systolic blood pressure: deleterious effects and implications for therapy. *J Cardiovasc Pharmacol Ther.* 2001;6:5)

that it is the large central arteries, rather than the peripheral vasculature, that undergo the greatest capacitance changes with age. Decreased compliance in the large arteries may also induce macrovascular damage in organs such as the kidneys and the brain once the “cushion” effect that absorbs systolic pulsations is lost, causing the microvasculature to be subjected to pulsatile flow. The microvasculature is generally considered to include the small arteries of less than 400 μm diameter, arterioles of less than 100 μm diameter and the capillaries with their single layer of endothelial cells. These distal vessels usually receive an almost constant, rather than pulsatile, blood flow. It is hypothesized that a more pulsatile microvasculature flow induced by age-related decline in the Windkessel effect, is a contributor to end-organ damage [8].

Input Impedance and Characteristic Impedance

Parallels have been suggested between the flow of blood in the arterial system and the flow of current within an AC electrical circuit [9]. An analogous electrical circuit would contain capacitors and resistors, with the alternating storage and discharge of the capacitor separating peak pressure and flow. The complex ratio that results from these values has two parts: the magnitude or “modulus” of the impedance and the “phase angle” that represents the number of degrees by which the sinusoidal pressure is separated from the sinusoidal flow. This combined single vector of “impedance” is often translated into arterial impedance. Impedance is defined as the relationship between the pressure difference and flow of sinusoidal signals in a linear system. However, it should be remembered that blood does not

behave sinusoidally, and so biological pressure and flow values must be converted into a fundamental sine wave and a series of harmonic waves using Fourier analysis prior to calculation of arterial input impedance (Z_m). A value for impedance is derived from each pair of sine waves of pressure and flow (i.e., harmonics) at their specific phase angle. To validly apply Ohm's law in this setting, the system should be in the steady state (vasomotor tone should be constant), time-invariant (free of beat-to-beat changes in resistance) and linear. The non-linearity of the ventricle during contraction does somewhat limit this technique, with the variations in elastance of the chamber during contraction being unaccounted for. Therefore, it would not be accurate to derive input impedance from invasive values for the left ventricular pressure and aortic flow, because the intervening aortic valve adds significant non-linearity. However, when considering the arterial tree, the variations in pressure and flow are minor enough to enable systemic and pulmonary arterial input impedance to be considered valid mathematical descriptions of the systemic and pulmonary arterial trees, respectively.

When using the impedance concept in a compliant vascular system, the flow will be advanced with respect to the pressure sine wave. This is depicted as -90° in the phase angle. With inertance the flow is delayed, giving a $+90^\circ$ phase angle. The modulus of impedance will decrease with increasing frequency. In a large elastic artery, the compliance and inertia effects interact to keep pressure and flow sine waves in phase. This gives a pulsatile or "characteristic" impedance with a phase angle of 0. In this setting the modulus will be constant and independent of changes in frequency. If the system were without reflection waves, the input impedance would equal the characteristic impedance. However the reflected waves moving retrogradely toward the proximal aorta result in a significant difference between arterial input impedance and the characteristic impedance, which incorporates the reflected waves. This difference is more apparent at lower frequencies, where reflected waves return out of phase. Conversely, at high frequencies the wavelengths are less than the arterial system length and so reflected waves are out of phase and cancel each other out. Therefore, at high frequencies, input impedance is almost equal to characteristic impedance [10]. The aortic input impedance spectrum gives information in the frequency domain about the arterial elastance, pulse wave reflectance, and the peripheral resistance. The clinical relevance is that increases in the pulsatile components—the elastance and reflectance—will lead to ventriculo-arterial mismatch and are therefore detrimental to cardiac efficiency (Fig. 2.3).

Assessing Afterload from Invasive Hemodynamics

Efforts to apply the impedance concept as a clinically measurable tool have been hampered by the complexity of the many advanced analytic functions required to derive values, and hence the much simpler mean aortic pressure or mean systolic pressure remains the more commonly used surrogate of afterload. It is customary to use the mean pressure value because this somewhat accounts for the fluctuations in aortic pressure that occur during the cardiac cycle. Clinically, the invasive measurement of cardiac afterload is usually achieved with a pressure tracing from a fluid-filled catheter with its tip lying just above the aortic valve in the ascending aorta.

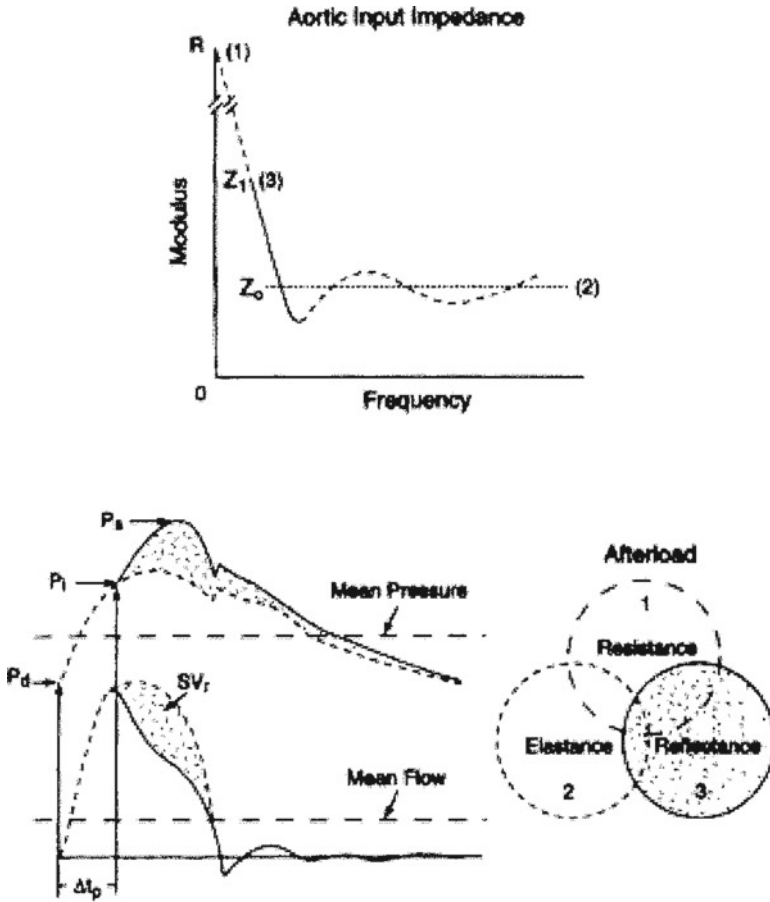


Fig. 2.3 The components of aortic input impedance (From Nichols WW, Edwards DG. Arterial elastance and wave reflection augmentation of systolic blood pressure: deleterious effects and implications for therapy. *J Cardiovasc Pharmacol Ther.* 2001;6:5)

One phenomenon that the clinician must bear in mind in this setting is the possibility of “pressure recovery.” This describes the increase of pressure downstream from a stenosis caused by reconversion of kinetic energy to potential energy, and can be a source of discrepancy between catheter and Doppler valvular pressure gradients. Bernoulli’s theorem, from which Doppler evaluations of flow across a stenosis can be derived, requires that the sum of the pressure head, potential energy, and kinetic energy must be equivalent throughout all parts of the flow system. Therefore, in the setting of aortic stenosis, the lowest pressure is found where the velocity is highest and hence where the valve orifice is the smallest. Beyond the stenosis, velocity decreases and so pressure will increase, with the total amount of pressure increase (pressure recovery) being dependent upon the dissipation of kinetic energy due to flow separation and vortex formation across the valve. The consequence is that when Doppler gradients are measured at the point of minimal diameter of the stream

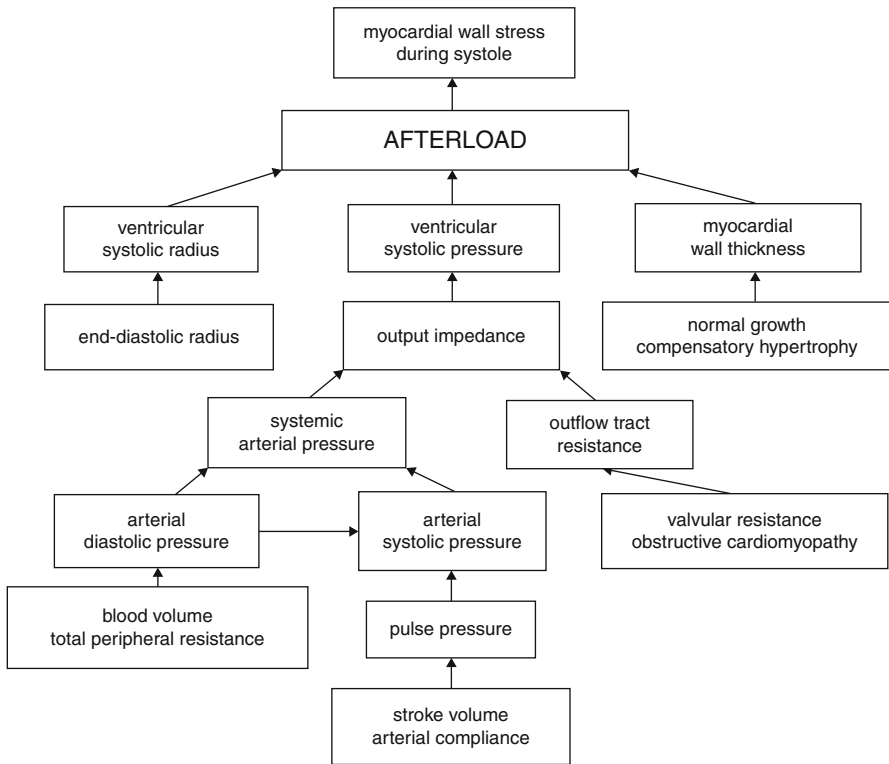


Fig. 2.4 Factors determining afterload (From Norton JM. Toward consistent definitions for pre-load and afterload. *Adv Physiol Educ.* 2001;25(1-4):53-61)

of blood flow (the “vena contracta”), they will be higher than the invasive catheter measurements obtained in the proximal aorta, where pressure has been recovered. It has been noted that in milder aortic stenosis the cusps of the valve form a funnel-shaped orifice and cause greater pressure recovery than in a more severely stenosed valve [11]. The extent of the phenomena is also dependent upon the relationship between the dimensions of the valve orifice and the ascending aorta. A smaller aorta will lead to a lesser pressure loss and hence increased pressure recovery, compared to a larger aorta with the same degree of aortic stenosis.

The complexity of the relationship between the contracting ventricle, the arterial system, and its blood flow is such that finding a single parameter to fully encompass the cardiac afterload is probably impossible (Fig. 2.4).

Ventricular Wall Stress Versus Arterial Input Impedance

As previously introduced, aortic input impedance is only one of two biophysical concepts available to define afterload; the other is ventricular wall stress, defined

by LaPlace as $PR/2w$. Wall stress also carries with it some clinical limitations, as the values for pressures and dimensions are instantaneous and cannot account for rapidly changing loads encountered during the cardiac cycle. The calculations are also highly dependent upon ventricular geometric assumptions. The two differing afterload approaches of input impedance and wall stress have been compared in their validity as indicators of ventricular performance. Ross et al constructed an animal model protocol to elucidate the relative importance of wall stress and impedance in negatively impacting ventricular stroke volume. These early experiments concluded that the dominant factor in regulating ventricular performance, as demonstrated by reduced fractional shortening, was the level of wall stress, rather than input resistance or pulsatile impedance [12].

Afterload Mismatch

Allied to this observation is the recognition that when pulsatile impedance is greater, changes in mean resistance produce greater changes in wall stress. This is presumably the result of the large increase in ventricular volume when pulsatile resistance rises, again emphasizing the impact of ventricular geometry on the outcome of these maneuvers. This appreciation led to the concept of “afterload mismatch” in 1976, as a framework for assessing the matching between the afterload and the inotropic state in the whole heart. Under normal physiologic circumstances, an increase in afterload is usually accompanied by increased venous return (due to movement of blood from the arterial to venous systems) and hence increased end-diastolic volume. This helps to maintain stroke volume in the face of an increased afterload. A mismatch can be induced acutely in a normal heart if end-diastolic volume is not allowed to compensate for the increase in afterload [13]. The result will be a fall in stroke volume, ejection fraction and ventricular circumference. An example of mismatch creation could be a scenario with sudden infusion of vasopressor into a volume depleted vascular system, or in the setting of partial inferior vena cava occlusion. An afterload mismatch can also be induced in a normal left ventricle in the opposite hemodynamic situation when the limit of preload reserve has already been reached and the average sarcomere length exceeds $2.2 \mu\text{m}$. Additional afterload applied to the ventricle already working at a maximal end-diastolic volume will cause a sharp drop in stroke volume, unless contractility is also enhanced by an inotrope. Thus an applied afterload stress can serve as an indicator that a heart is operating near either the upper or lower limits of preload [14]. The concept that afterload mismatch can exist even in the basal state explains why therapeutic afterload reduction in conditions such as severe left ventricular dysfunction or mitral regurgitation can significantly improve cardiac output, so long as preload is maintained.

In addition to the acute afterload response studies on the intact heart in unanesthetized large animal subjects, the longer term effects of a sustained increase in afterload have also been extensively studied in animal models. Ross et al. instrumented 12 dogs with ultrasound transducers placed across the left ventricle for measuring

the extent and velocity of wall shortening, and a micromanometer measuring left ventricular cavity pressure. Transaortic constriction was performed using an inflatable rubber cuff around the proximal aorta to maintain an average systolic blood pressure of 210 mmHg. Ventricular pressures and dimensions were recorded prior to constriction, immediately after constriction, at an early phase after constriction (average 9 days) and a later phase (average 2.5 weeks). Calculations of wall forces relied on a spherical model. Immediately after constriction there was a decrease in ventricular wall thickness, and a 55% increase in calculated peak wall stress above control. Percentage shortening fell by 24% acutely and mean circumferential shortening velocity (V_{CF}) decreased by 39% from control. In the acute phase (mean 9 days) the ventricles were seen to dilate with a 4% increase in end-systolic diameter and peak wall stress fell to 37% above control despite a constant peak systolic left ventricular pressure averaging 210 mmHg. Percentage shortening and mean V_{CF} remained below control levels at -12 and -20% respectively. By the later phase at mean 2.5 weeks, the left ventricular walls had significantly hypertrophied with a 15% increase in ventricular wall crosssectional area above control, with the increased wall thickness successfully reducing peak wall stress to 22% above control. End-diastolic diameter and percent shortening returned to normal [14]. The ventricle was considered to have successfully compensated at this time point by resuming its baseline fractional shortening in the face of a marked sustained elevation in afterload. This study reinforces the concept that the initial afterload mismatch, which causes an acute reduction in stroke volume, can be overcome by the development of physiological hypertrophy with thickened walls once again generating baseline stroke volumes. However, the limited duration in this early proof of concept study does not permit observation of the rapidly hypertrophied heart as it continues to maintain the higher degree of pressure generation against an increased afterload over time. The technique of transaortic banding has been applied to many species of experimental animal models, most commonly mice, enabling investigators to study the development to physiological hypertrophy and, in some settings, subsequent progression to heart failure, so elucidating the myocardial signaling pathways that govern the hypertrophic response [15].

Ventriculo-Arterial Coupling and Pressure-Volume Loops

The relationship between the ventricle and its afterload is key to the concept of ventriculo-arterial coupling, and can be illustrated by pressure-volume loops. The effective arterial elastance (E_a) describes the ability of the vessel to accommodate pulsatile flow. E_a can be calculated by dividing the end-systolic pressure by the stroke volume and is therefore the slope of the stress/strain or pressure/diameter graphs ($\Delta P/\Delta D$). Elastance is the reciprocal of compliance, compliance being the ease of distension. At lower levels of arterial pressure, the arterial wall is supported by compliant elastin fibers, whereas the stiffer collagen fibers predominate at higher pressures. Therefore the slope of the curve will be greater at higher levels of arterial pressure. Collagen in the human aorta is at least 500 times stiffer than elastin and more than double in aortic wall composition from age 20 to 70 years (Fig. 2.5).

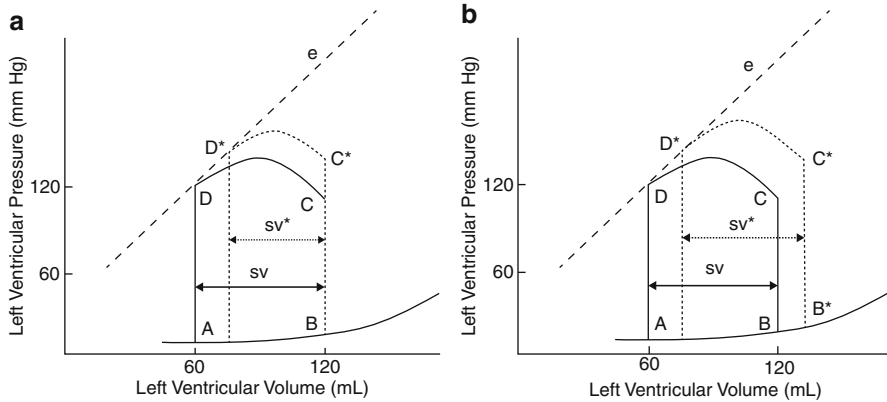


Fig. 2.5 Effects of acutely increasing afterload on the pressure-volume loop (From Loushin MK, Quill JL, Iaizzo PA. *Mechanical Aspects of Cardiac Performance*. In: Iaizzo PA, editor. *Handbook of Cardiac Anatomy, Physiology, and Devices*. 2nd ed. New York: Springer; 2009. p. 271–296)

During the left ventricular ejection phase of the cardiac cycle, as ventricular volume decreases, the potential for the ventricle to develop pressure also drops. The smallest volume reached is the end-systolic volume, at which point the whole stroke volume has been ejected. The aortic valve subsequently closes and the diastolic phase begins. The end-systolic volume at a certain degree of contractility and preload will therefore be determined by the afterload. A rise in aortic pressure, all else being equal, will correlate with a decreased stroke volume and a lower aortic pressure with an increased stroke volume. For example, in an individual with aortic stenosis, the pressure-volume loop may show a higher peak pressure, a lesser stroke volume, and an increased end-systolic volume, so shifting the curve into a taller and narrower configuration. Over time, compensatory hypertrophy will mitigate the high wall stress and improve the ventricle's ability to overcome the high afterload and increase the stroke volume, thus causing the loop to increase in width. With a sudden increase in afterload the stroke volume will be diminished, which causes the end-systolic volume to rise. Over the following few beats the increase in end-systolic volume predominates over the increased end-diastolic volume (which usually augments ventricular function), with the net change being a decrease in stroke volume and hence a decrease in the width of the pressure-volume loop. With a reduced afterload, the left ventricle ejects blood with greater ease, so augmenting the stroke volume and decreasing end-systolic volume. With less blood remaining in the ventricle after the ejection phase, the ventricle will fill to a lesser end-diastolic volume compared to prior to the afterload reduction. Despite this mild reduction in preload, stroke volume shows a net increase because the reduction in end-diastolic volume is less than the reduction in end-systolic volume.

The ratio of the effective arterial elastance to the E_{es} (which is the slope of the ventricular end-systolic pressure-volume line) represents a measure of pump efficiency in expelling blood into the vasculature. This value can be used as a reflection of the ventriculo-arterial coupling and helps conceptualize the relationship between the pump and the vasculature. As E_a increases initially, the arteries accommodate greater

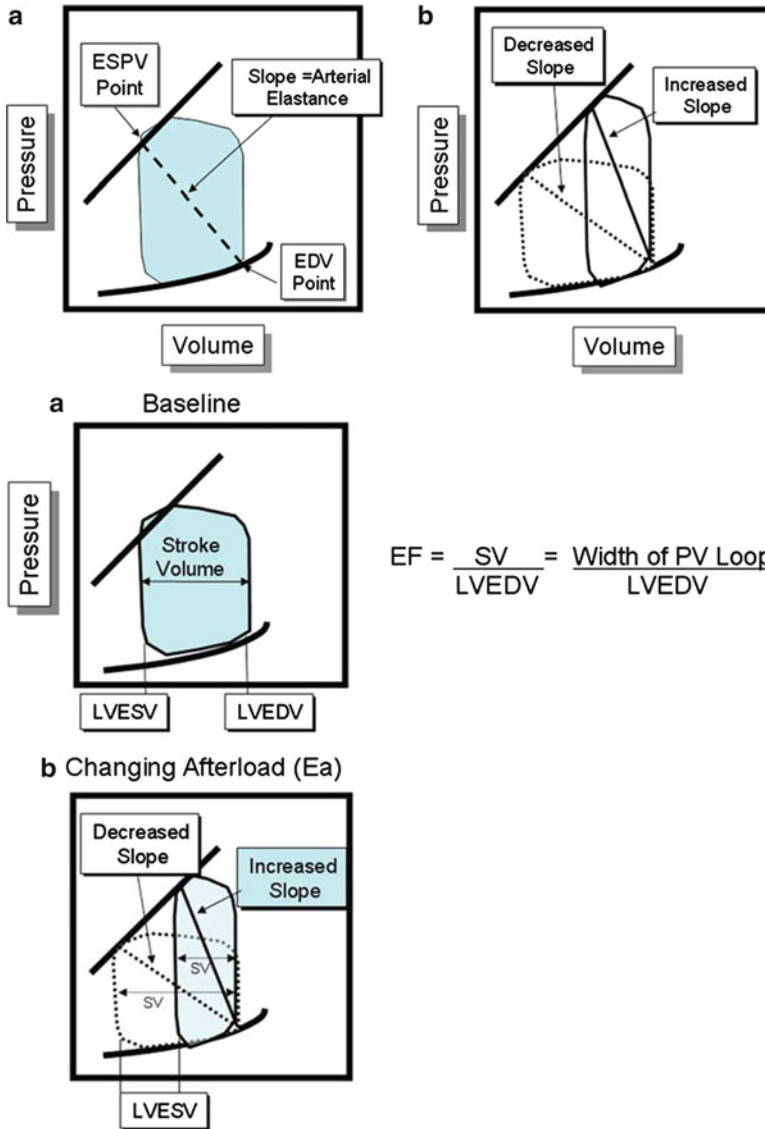


Fig. 2.6 The pressure-volume relationship and elastance (From Bashore TM. Clinical Hemodynamics in Valvular Heart Disease. In: Wang A, Bashore TM, editors. Valvular Heart Disease. New York: Humana-Springer; 2009. p. 93–122)

blood flow, permitting a greater stroke work. If E_a were to continue to increase, the stroke work would reach a maximal plateau value where arterial and ventricular properties are equal, meaning that $E_a = E_{es}$. The E_a also increases with improvements in ventricular efficiency, which is defined by external stroke work/ MVO_2 /beat. Ventricular efficiency is maximal at $E_a = E_{es} / 2$, meaning that the most favorable ventriculo-arterial coupling occurs when the E_a/E_{es} ratio lies in the range 0.5–1.0 [16] (Fig. 2.6).

Afterload and Cardiac Efficiency

The heart requires significant energy generation to perform its functions. Cardiac metabolism is predominantly aerobic, and hence the work performed by the heart is typically gauged in terms of myocardial oxygen consumption (MVO_2). Myocytes are densely packed with mitochondria to generate sufficient ATP, predominantly from fatty acid breakdown, to fulfill the required cellular mechanics to sustain the cardiac cycle. The energy required for development and maintenance of systolic wall tension is a key factor in determining myocardial energy expenditure. One hallmark of the failing heart is its disordered and inefficient myocardial metabolism. The degree of afterload is also highly relevant in the ischemic heart, where reducing afterload and reducing heart rate are the major strategies in reducing myocardial oxygen consumption. A systolic pressure increase of only 20–30 mmHg can have a dramatic negative impact on function in a failing or ischemic left ventricle, both by inducing a lower stroke volume and by raising myocardial oxygen demands. Oxygen extraction in the capillary bed is near-maximal and hence the capacity to meet the oxygen demands of the myocardium may not be possible in the setting of a high afterload, especially if coronary blood flow can no longer be increased due to flow-limiting stenoses. The other determinants of myocardial oxygen demand are the heart rate, preload, and contractility. The MVO_2 in the resting heart is approximately 8 mL O_2 /min per 100g [17]. The instantaneous cardiac oxygen consumption can be measured in a human heart by employing the Fick principle; however, this does require catheterization of the coronary sinus to directly measure the venous oxygen saturation and coronary blood flow. Therefore indirect assessments of the MVO_2 are necessary. Relative changes can be estimated by calculating the pressure-rate product. A simple method, described as early as 1912 using isolated cat and rabbit myocardium is multiplication of the heart rate with the systolic blood pressure [18]. This noninvasive hemodynamic determinant of oxygen consumption has been validated by other investigators using the isolated dog heart, with the aortic pressure being shown to be the dominant influence in determining myocardial oxygen requirement. A 175% increase in work with afterload elevation was matched with a 178% increase in oxygen consumption as calculated by the product of coronary flow and coronary arteriovenous oxygen difference [19]. These investigators also established the use of the time-tension index/beat in mmHg seconds, derived from the area under the systolic portion of the aortic pressure curve, as an alternate metric of oxygen consumption. They also point out, by the Law of LaPlace, that the generation of the same intraventricular time-tension index will require greater myocardial fiber tension in a large radius heart compared to a smaller one. This fact highlights the inherent mechanical inefficiency of the dilated failing heart. Also of note is a study using healthy humans that demonstrated a correlation of 0.88 between MVO_2 and heart rate alone and 0.90 using the rate-pressure product [20], although some authors have emphasized the limitations of these indirect indices of MVO_2 which do not capture all potentially important changes in myocardial contractility and ventricular dimensions, particularly in less healthy subjects [21].

The Law of LaPlace can also be used to explain why the pressure-overloaded left ventricle (such as that associated with aortic stenosis) will incur a higher myocardial

oxygen demand than the volume-overloaded ventricle (as in aortic regurgitation). LaPlace stated that wall tension is proportional to $PR/2$, where P is chamber pressure, and R is chamber radius. The pressure-overloaded ventricle shows a large increase in the pressure variable, which will equate to much higher wall tension, and hence MVO_2 . Conversely, in the volume-overloaded ventricle the radius will increase, but not as dramatically as the pressure in the pressure-overload model. Hence the rise in wall stress in the volume overload setting will be less substantial, and the corresponding MVO_2 less dramatically elevated.

Afterload in Clinical Practice

Afterload in the Pulmonary Vasculature

Afterload is most frequently discussed in reference to the left ventricle, but can also be applied to the right ventricle and the pulmonary vasculature into which this chamber pumps. It should be noted that significant differences exist in the manners in which the right and left ventricle handle increases in their afterloads. Normally the resistance to flow in the pulmonary vascular system is much lower at about one-tenth of the resistance met by the left ventricle for the same stroke volume. The thicker walled left ventricle is able to generate much greater pressures and usually successfully generates unchanged stroke volumes in the face of afterload increases. The right ventricle operates much nearer to its full contractility capacity, because it has only a sixth of the muscle mass of the left ventricle and yet performs a quarter of the work. It succeeds in pumping the same cardiac output as the left ventricle due to the much lower resistance in the pulmonary vasculature than the systemic circulation. Operating within this closely matched ventriculo-arterial framework, the right ventricle is extremely sensitive to elevations in its afterload. Even a structurally normal right ventricle may decrease its stroke volume to small elevations in pulmonary vascular resistance. However, the right ventricle can also remodel and adapt to higher pulmonary pressures with time, with the maximal mean artery pressure normally accommodated without right ventricular failure being in the order of 40 mmHg. Severe right ventricular dilatation and dysfunction usually results from its attempts to compensate and maintain stroke volume as the pulmonary pressures rise beyond this [22].

- The pulmonary arterioles also serve as the site of major resistance to flow; however, the pulmonary arterioles receive a more pulsatile input of blood flow than their systemic counterparts. Within this much smaller vascular system, the roles of cushion, conduit, and resistance are not as clearly ascribed to certain generations of vessels as in the systemic circulation. Pulmonary hypertension is currently defined as a mean pulmonary artery pressure of greater than 25 mmHg with a pulmonary capillary wedge pressure less than 15 mmHg [23]. The various etiologies of pulmonary hypertension all tend to show common histopathology

features, namely initial fibrosis, medial thickening, and pulmonary arteriolar occlusion [24]. Right ventricular afterload reduction with pulmonary vasodilators is key to the management of pulmonary hypertension and right ventricular failure. Inhaled nitric oxide has a role during the invasive assessment of pulmonary vascular pressures to help determine the potential for pulmonary vasodilatation, and the use of continuous oxygen therapy can help reduce the degree of hypoxic vasoconstriction. Pulmonary hypertension therapeutics include calcium channel antagonists (nifedipine, amlodipine), prostacyclin analogs (epoprostenol, treprostinil, iloprost), endothelin receptor antagonists (bosentan, ambrisentan), and phosphodiesterase-5 inhibitors (sildenafil) [25].

Afterload and the Respiratory Cycle

The potential for mechanical ventilation to affect invasive assessments of preload (such as the right atrial and pulmonary capillary wedge pressures) and possibly reduce preload by decreasing the pressure gradient into the thorax was discussed in Chap. 1. Positive pulmonary pressures during mechanical ventilation also affect afterload. The degree of pulmonary vascular resistance, and hence RV afterload, is proportional to the degree of airway pressure elevation. With significant RV afterload elevations the right ventricle will dilate and induce intraventricular dependence, with shifting of the septum into the left ventricle, which reduces left ventricular filling and stroke volume. Conversely, the direct effect of positive airway pressure on the left ventricle is to increase stroke volume by increasing the intrathoracic aortic pressures relative to peripheral arterial pressure. Also worth mentioning in the consideration of valvular lesions and afterload is the effect of mitral regurgitation on the degree of cardiac afterload. Mitral regurgitation will decrease afterload because, during ventricular systole, a fraction of the left ventricular end-diastolic volume will take a retrograde route and flow back into the left atrium through the incompetent valve. Hence the left ventricle will be working against a reduced afterload, as some blood ejection is into the lower-pressure atrium rather than the usual anterograde flow into the higher-pressure aorta.

Total Peripheral Resistance

The term “total peripheral resistance” (TPR) encompasses the sum of all regional resistances in the systemic circulation. It is sometimes used to infer the total afterload faced by the heart, although as we have already seen the resistance to flow, largely imposed by the arterioles, is actually only one component of the complete cardiac afterload. TPR can be approximated from Ohm’s law. In the patient with Swan-Ganz calculations of cardiac output, values for systemic vascular resistance

(SVR) and pulmonary vascular resistance (PVR) are routinely derived in Wood units from:

$$\text{SVR} = 80 \times (\text{mean arterial pressure} - \text{mean right atrial pressure}) / \text{cardiac output}$$

$$\text{PVR} = 80 \times (\text{mean pulmonary artery pressure} - \text{pulmonary capillary wedge pressure}) / \text{cardiac output}$$

These equations give values in dyn s cm^{-5} . Other units for measuring vascular resistance are pascal seconds per cubic meter (Pa s/m^3), or for convenience when using pressure in mmHg and cardiac output in l/min resistance can be expressed in mmHg min/L. This equates to hybrid reference units (HRU), also known as Wood units, favored by pediatric cardiologists. Multiplying by a factor of 8 converts from Wood units to MPa.s/m^3 , or by a factor of 80 to convert from Wood units to the international unit of dyn.s.cm^{-5} .

The resistances imposed by the arterial system are arranged in both serial and parallel orientations. In a circuit where resistances lie in series, the total resistance will be the sum of the individual resistive components. Conversely a parallel circuit will have a total resistance equaling the sum of the reciprocals of the individual resistive components, thus creating a much lower overall resistance than in a series circuit. Therefore, most organ arterial supplies are configured in a parallel arrangement, so limiting the pressure generation required by the ventricle to perfuse all organs. A rise in resistance within one organ bed will have minimal impact on the other arterial beds.

The majority of the resistance component of arterial input impedance lies in the arterioles. These vessels range from 10 to 150 μm in diameter and are under constant vasoactivity regulation from the sympathetic nervous system and local mediators, thus controlling the flow of blood into specific capillary beds. Local vasodilators include platelet-derived substances such as serotonin, and endothelium-derived mediators such as nitric oxide.

Therapeutic Afterload Reduction

The concept of therapeutic afterload reduction was initially clinically applied in the form of intra-aortic balloon counterpulsation to support patients with cardiogenic shock post myocardial infarction. This technique was demonstrated to unload the left ventricle, enhance left ventricular ejection fraction, and improve coronary artery perfusion. Pharmacological strategies for unloading the left ventricle, principally the use of a sodium nitroprusside infusion, have also become useful tools in acute cardiac care. Nitroglycerin, which combines more venodilation with arteriolar vasodilation in comparison to nitroprusside, may also be used for afterload reduction. Hydralazine and the ACE inhibitors are additional options. Vasodilating drugs have little direct effect on the large elastic arteries, but can markedly reduce the amplitude of reflected waves from the periphery. The decreased amplitude and velocity of the reflected wave results in a general decrease in systolic arterial pressure and increased proximal aortic flow during the deceleration phase. The resulting afterload reduction can help to optimize

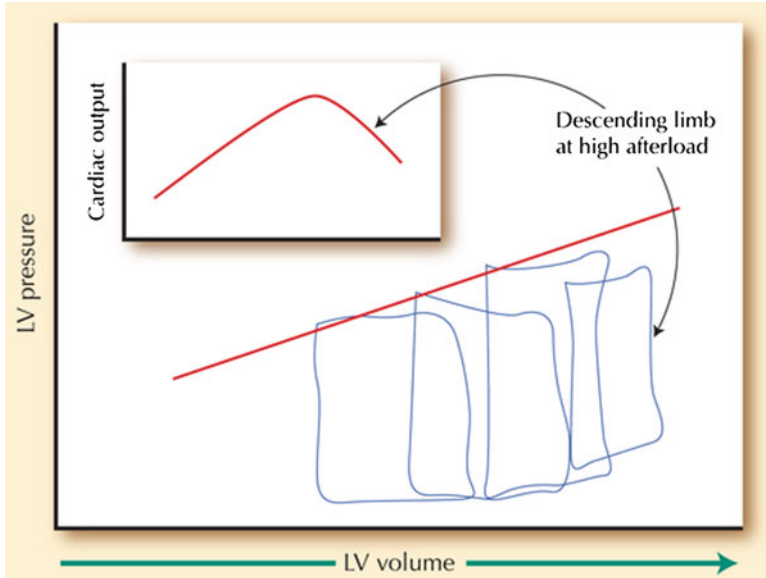


Fig. 2.7 Conditions for afterload mismatch in systolic heart failure (From Ross J, Jr. Afterload mismatch and preload reserve: a conceptual framework for the analysis of ventricular function. *Prog Cardiovasc Dis.* 1976; 18:255–264)

cardiac output and clinical status in patients with cardiogenic shock, severe mitral or aortic regurgitation, or even aortic stenosis with decompensated left ventricular dysfunction[26], by correcting the afterload mismatch. The afterload tends to be high in decompensated heart failure due to activation of the renin-angiotensin-aldosterone system, as well as a higher effective blood velocity due to slow forward flow. Although the sympathetic activation causing vasoconstriction in heart failure is compensatory to maintain arterial blood pressure despite low output, these adaptations can be counterproductive and impose further afterload on the failing ventricle. Pharmacological afterload reduction can therefore achieve marked improvements in cardiac output and symptoms (Fig. 2.7).

The use of afterload reduction in patients with aortic stenosis may initially seem counterintuitive as the cardiac output across a stenotic aortic valve has traditionally been considered to be fixed with a risk of hypotension without improvements in output if the blood pressure is lowered. However, this scenario underlines the complexity of afterload, because the aortic stenosis is not actually the sole factor determining the force against which the ventricle must pump. Resistances in series are additive, and so the resistive component of aortic input impedance can still be lowered by reducing the most distal resistances in the arterioles despite the proximal resistance across the valve remaining constant. The reduction in total peripheral resistance and hence mean arterial pressure with nitroprusside can therefore successfully reduce the afterload mismatch of the dysfunctional ventricle pumping against a high afterload despite the presence of severe and fixed aortic stenosis. Conversely, the administration of nitroprusside to a

relatively normal cardiovascular system, or to the heart with aortic stenosis but a preserved ejection fraction, would be expected to lower the cardiac output. This is due to some concurrent venodilation, which will reduce preload and actually induce an afterload mismatch. Another setting where pharmacological afterload reduction can precipitate a worsened clinical status is in the setting of a significant pulmonary shunt. Nitroprusside can inhibit the hypoxic vasoconstriction in a region of pulmonary vasculature, thus supplying blood flow to an area of the lung not receiving good oxygenation (for example due to lobar consolidation). This will exaggerate a perfusion-ventilation mismatch and potentially worsen the arterial oxygen saturation. The use of nitroprusside as a lone afterload reducer in the setting of ischemia should also be avoided. Nitroprusside has been shown to decrease myocardial perfusion in the setting of coronary stenoses, whereas nitroglycerin can enhance myocardial perfusion, largely through dilatation of coronary collateral vessels [27].

Bullet Point Summary

- Afterload consists of the forces against which the heart pumps to expel blood into the vasculature.
- Afterload can be defined in terms of wall stress, using the law of LaPlace.
- Alternatively, afterload can be conceptualized as arterial input impedance, drawing parallels from electrical circuits.
- An inverse relationship exists between stroke volume and afterload.
- The aorta and proximal large arteries have a higher ratio of elastic to collagen and are therefore highly compliant.
- These elastic arterial walls absorb the systolic pulsations in blood flow, converting stored energy into recoil that maintains the pressure and flow during diastole—the Windkessel effect.
- The arterioles are the site of the majority of arterial resistance, with arteriolar tone being highly dependent on the sympathetic nervous system and local mediators.
- Reflected waves from bifurcations and arterial discontinuities can increase afterload when they return to the proximal aorta during systole.
- With aging, or pathological processes such as hypertension, afterload rises due to increased magnitude of the incident systolic wave and also early return of the reflected wave.
- Afterload mismatch is a scenario in which the ventricular performance is not well coupled to the afterload it encounters, which increases myocardial oxygen consumption and decreases cardiac energy efficiency.
- Over time, an afterload mismatch can induce ventricular hypertrophy.
- Intra-aortic balloon counterpulsation, nitroprusside, and ACE inhibitors can decrease systemic afterload.
- Pulmonary vasodilators are the cornerstone of pulmonary hypertension management and decrease the afterload faced by the right ventricle.

Review Questions

1. The primary determinant of cardiac output is:

- a) Preload
- b) Myocardial contractility
- c) Heart rate
- d) Afterload

Answer is a).

2. Which one of the following statements regarding the vasculature is *false*?

- a) With aging, medial degeneration of the large elastic arteries causes them to stiffen
- b) Vascular compliance is heart rate dependent
- c) The small peripheral vessels show a prominent “Windkessel effect”
- d) Retrogradely reflected pressure waves usually arise from arterial branch points such as the iliac bifurcation
- e) A reflected wave falling during diastolic is more advantageous to the cardiovascular system

Answer is c). It is the proximal elastic arteries that show the “Windkessel effect.” The smaller peripheral arteries and arterioles have the capacity to vasoconstrict substantially, but are not exposed to highly pulsatile blood flow and do not have the elastic properties to permit significant recoil if the pressure within the vessel falls. A reflected wave falling within diastole can help to augment coronary blood flow.

3. Which one of the following statements is true regarding the concept of “afterload mismatch”?

- a) Afterload mismatch can occur when the patient is vasodilated
- b) An increase in afterload is usually accompanied by a decrease in venous return, due to decreased availability of blood in the venous system
- c) Afterload mismatch may occur with sudden infusion of vasopressor in the setting of volume depletion
- d) Afterload mismatch can be induced in a normal left ventricle with high preload, when a sudden increase in both afterload and myocardial contractility occurs
- e) A chronic afterload mismatch does not result in structural myocardial changes

Answer is c). Under normal physiologic circumstances, an increase in afterload is usually accompanied by increased venous return, due to movement of blood from the arterial to venous systems. A mismatch can be induced acutely in a normal heart if end-diastolic volume is not allowed to compensate for the increase in afterload. Alternatively, additional afterload applied to a ventricle already working at a maximal end-diastolic volume will cause a sharp drop in stroke volume, unless contractility is also enhanced.

4. Which one of the following statements is true regarding potential strategies to reduce afterload clinically?
- a) The goal of intra-aortic balloon counterpulsation is to lower systolic blood pressure and hence reduce afterload
 - b) In the setting of some pulmonary conditions, nitroprusside can cause hypoxia
 - c) Afterload reduction is strictly contraindicated in the setting of a fixed obstructive lesion such as aortic stenosis
 - d) The sympathetic activation causing vasoconstriction in heart failure is compensatory to maintain blood pressure despite low cardiac output, and hence afterload reduction should be avoided
 - e) Sildenafil is a selective pulmonary arterial vasodilator and has no effect on the systemic vasculature

The answer is b). Nitroprusside can inhibit the hypoxic vasoconstriction in a region of pulmonary vasculature, thus supplying blood flow to an area of the lung not receiving good oxygenation (for example due to lobar consolidation). This will exaggerate a perfusion-ventilation mismatch and potentially worsen the arterial oxygen saturation. Intra-aortic balloon counterpulsation augments diastolic blood pressure, thus reducing left ventricular wall stress. Afterload reduction with an IABP or nitroprusside may be indicated in acutely ill patients with severe aortic stenosis and a reduced left ventricular ejection fraction. Vasodilation in the setting of decompensated systolic heart failure can correct an afterload mismatch and improve the cardiac output. Sildenafil does have some peripheral vasodilating effects, and hence dosage may be limited by systemic hypotension.

5. A 70-year-old with severe aortic stenosis (peak/mean pressures by echocardiography 68/42, aortic valve area by continuity equation 0.6 cm²) presents with worsening dyspnea, lower extremity edema, oliguria, and a 15 lb weight gain. The blood pressure is 88/74. He is peripherally cool and mildly confused. The left ventricular ejection fraction on his most recent echo was 25%. Are the following statements true or false?
- a) Due to the severity of the aortic valve stenosis, the only option for reducing afterload is to valvuloplasty or valve replacement.
 - b) There is an afterload mismatch.
 - c) Pressure recovery may lead to overestimation of the valve gradient by Doppler measurements, and is more likely to occur with smaller ascending aorta diameter.
 - d) The calculated SVR is likely to be elevated; a lower than expected SVR may suggest a septic component to the hypotension.
- a) False. The total resistance presented by the arterial system is a sum of the many components arranged in series through the vasculature. The significant resistive contribution provided by the arterioles is additive to the resistance imposed by the stenotic valve. Therefore, the afterload can be reduced by vasodilatation of the arterioles.

- b) True. Although we do not have invasive hemodynamics provided for this patient, the cool peripheries, delayed mentation and oliguria strongly suggest a low cardiac output state. Therefore, the poor ventricular performance is not well matched to the high afterload imposed by the aortic stenosis plus peripheral vasoconstriction due to activation of the rennin-angiotensin system in cardiogenic shock. Better matching of the low stroke volume may be achieved through peripheral vasodilatation, if this can be tolerated by the low blood pressure. Aortic balloon counterpulsation, and/or low doses of intravenous nitropruside may be successful in improving the cardiac output and stabilizing the decompensated patient ahead of definitive aortic stenosis management.
- c) True. Pressure recovery is a phenomenon arising from the decrease in velocity and increase in pressure in the proximal aorta, beyond the stenotic aortic valve. This can lead to overestimation of the valve gradient by Doppler measurements, and is more likely to occur with smaller ascending aorta diameter.
- d) True. As described above, the systemic vascular resistance would be expected to be at the higher end, or above, the normal range for SVR. A value in the range of 1,200–2,500 dyn s/cm⁵ would be consistent with the scenario. If the calculated value lies much below this, consideration should be made of an additional distributive shock process, such as sepsis. Of note, a patient with cardiogenic shock and a poor cardiac output can sometimes be seen to have an encouraging rise in their mixed venous saturation, cardiac output and a fall in the SVR, with the actual etiology being early sepsis causing peripheral vasodilatation.
6. A 55-year-old female with hypertension, diabetes, and chronic kidney disease presents acutely dyspneic. Her blood pressure is 210/110, heart rate 92 bpm. Her examination is consistent with pulmonary edema. A diagnosis of hypertensive emergency is made. Are the following statements true or false?
- a) The decrease in arterial compliance associated with hypertension and diabetes is most pronounced in the arterioles.
- b) Effective arterial elastance is calculated by dividing the stroke volume by end-systolic pressure.
- c) If the mean arterial pressure is known to be 143 mmHg and the cardiac output 4.0 L/min, the systemic vascular resistance will calculate in the region of 2,500 dyn s/cm⁵.
- d) If this patient receives an arteriovenous fistula in preparation for future hemodialysis, the afterload would be expected to fall and the preload increase.
- a) False. The arteriosclerosis associated with hypertension and diabetes is most prominent in the large elastic arteries. The enhanced incident wave increases afterload, as does the early return of reflected pressure waves.
- b) False. Effective arterial elastance is calculated by dividing the end-systolic pressure by the stroke volume. It is visualized as the slope on the stress/strain graph.

c) True. $MAP = ((2 \times \text{diastolic pressure} + \text{systolic pressure})/3) = 143$. $SVR = 80 \times (MAP - RA \text{ pressure})/\text{cardiac output} = 80 \times (143 - 15)/4 = 2,560$.

d) True. Creation of a shunt from the arterial to venous system would be expected to decrease the afterload by directing blood flow away from the high resistance arterioles into the lower resistance venous system, and so enhancing venous return to the heart. The decreased afterload has been shown to slightly reduce myocardial oxygen demand, but also negatively impacts the coronary blood flow [27].

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Suggested Reading

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