UNDERSTANDING LEFT VENTRICULAR FUNCTION AND HEMODYNAMICS

Kenneth Alonso, MD, FACP

Blood flow and myocardial contraction

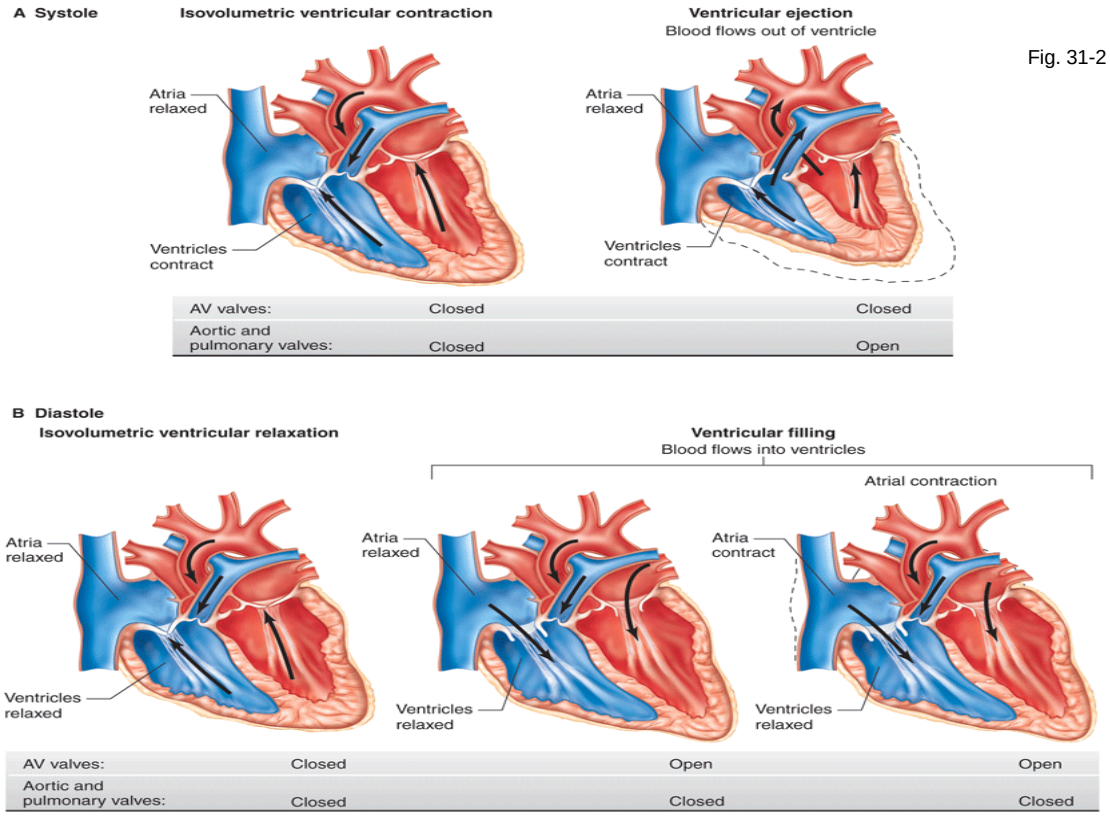


Fig. 31-2 Accessed 02/01/2010

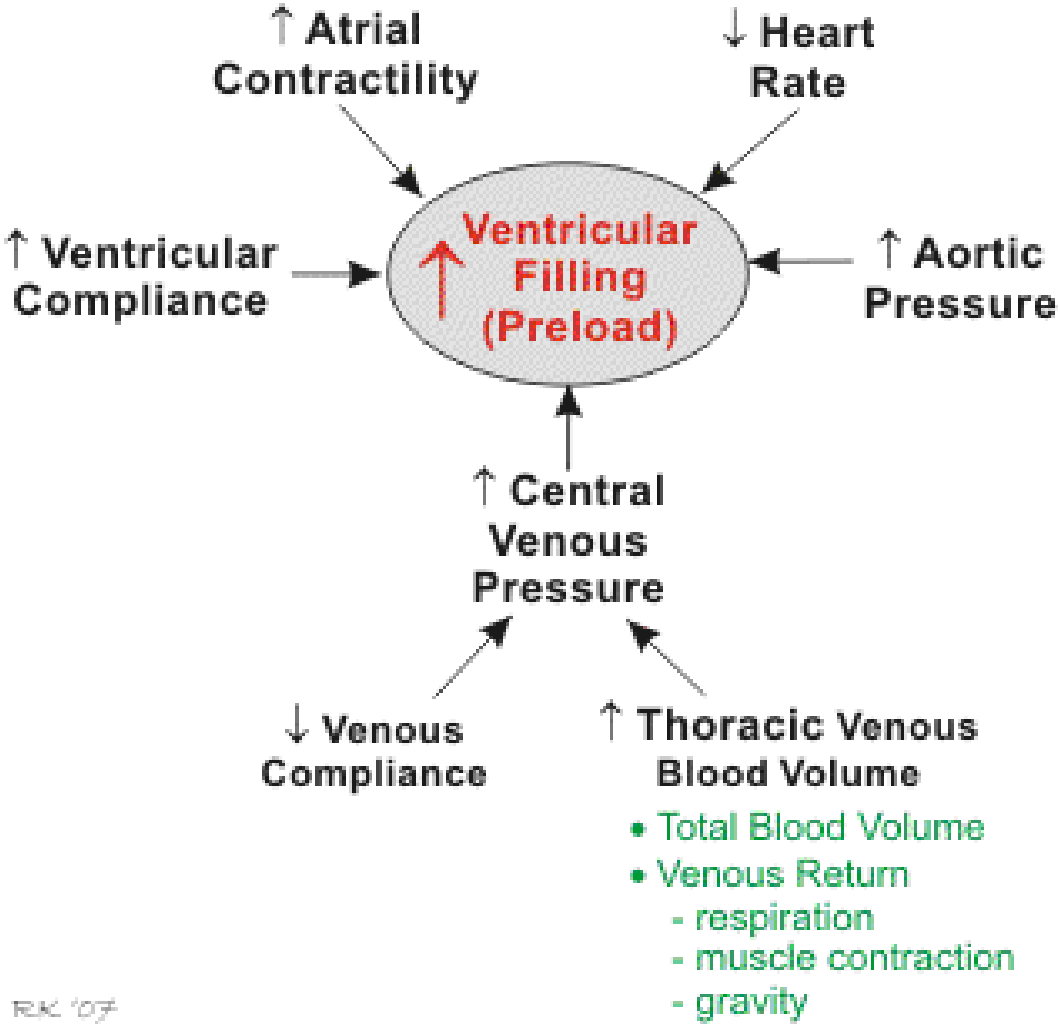
Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

Myocardial contraction

- Fundamental to cardiac muscle function are the relationships between force and muscle length, velocity of shortening, Ca^{2+}, and heart rate.
- The maximal force developed at any sarcomere length is determined by the degree of overlap of thick and thin filaments (the number of available cross-bridges).
- The ascending limb of the length–tension relationship (equivalent to the Frank-Starling relationship that relates preload to cardiac performance) is also caused by a length-dependent increase in myofilament Ca^{2+} sensitivity

Preload

- Preload can be defined as the initial stretching of the cardiac myocytes prior to contraction.
- Preload, therefore, is related to muscle sarcomere length.
- When venous return to the heart is increased, the end-diastolic pressure and volume of the ventricles are increased, which stretches the sarcomeres, thereby increasing their preload.
- Increasing preload increases the active tension developed by the muscle fiber and increases the velocity of fiber shortening at a given afterload and inotropic state.



https://www.cvphysiology.com/Cardiac%20Function/CF007

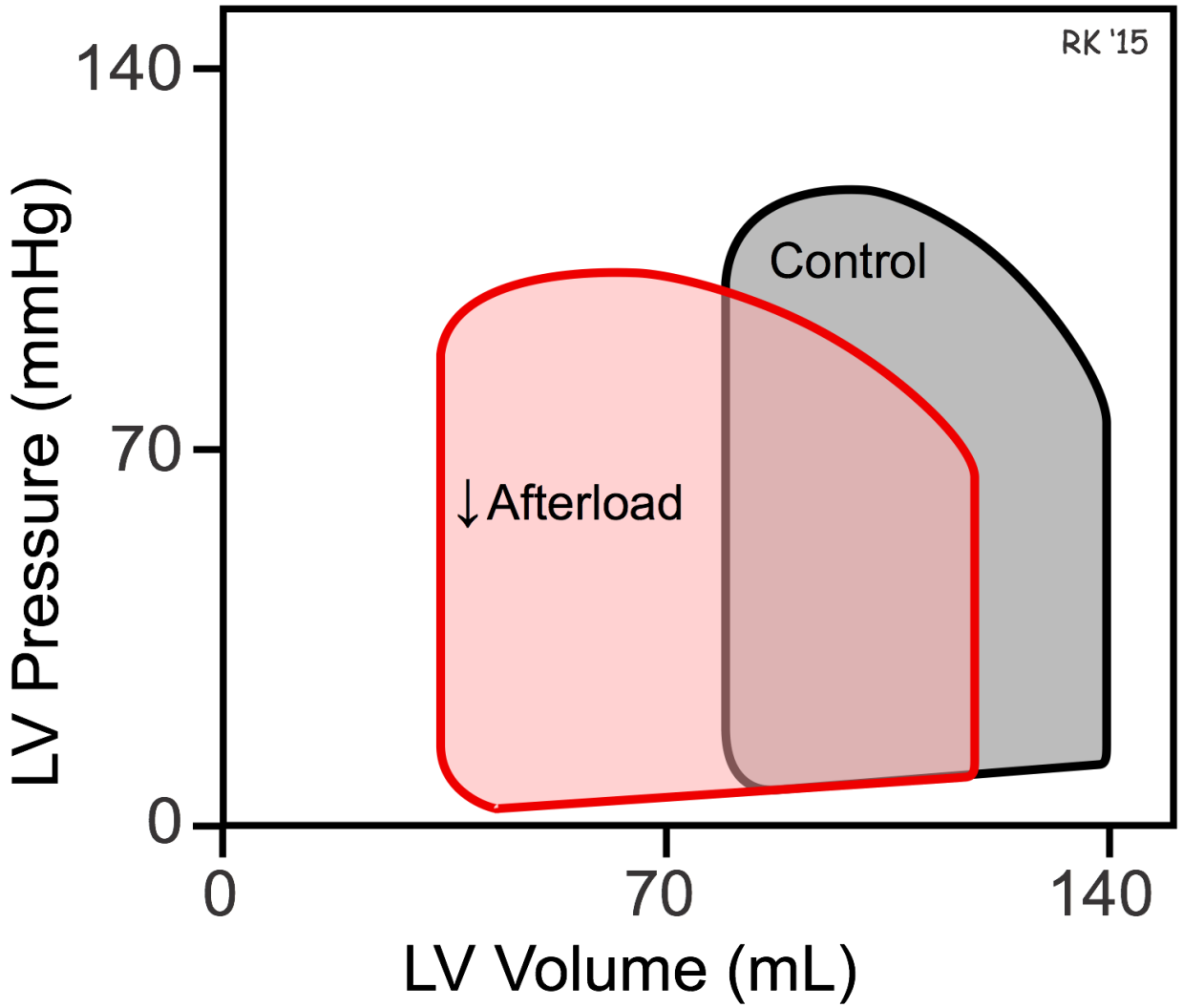
Afterload

- Afterload is the tension or stress in the ventricular wall during injection.
- This resistance to outflow) of the left ventricle is closely related to the aortic pressure.
- Afterload is often expressed as ventricular wall stress:
- $Pr/2h = \sigma$ (but is geometry dependent)
- Resistance of the vascular system = ΔP across the arterial circuit / cardiac output or mean flow = 8μ (viscosity of blood) Length of the arterials system $/\pi r^4$
- Wall stress is wall tension divided by wall thickness

Afterload

Wall stress and therefore afterload are increased by an increase in ventricular inside radius (ventricular dilation).

A hypertrophied ventricle, which has a thickened wall, has less wall stress and reduced afterload.



https://www.cvphysiology.com/Cardiac%20Function/CF008

Frank-Starling mechanism

- The ability of the heart to change its force of contraction and therefore stroke volume in response to changes in venous return
- Afterload per se does not alter preload
- However, preload changes secondarily to changes in afterload.
- Increasing afterload not only reduces stroke volume, but it also increases left ventricular end-diastolic pressure (LVEDP)
- Increases preload

Frank-Starling mechanism

- Increased preload in the normal heart leads to stretching of the myocyte (sarcomere)
- End-diastolic volume increases while pressure is held constant
- Increasing the sarcomere length increases the calcium sensitivity of Troponin C
- The rate of cross-bridge attachment and detachment increases
- The amount of tension developed by the muscle fiber increases

Frank-Starling mechanism

- This occurs because the increase in end-systolic volume (residual volume remaining in ventricle after ejection) is added to the venous return into the ventricle and this increases end-diastolic volume.

Myocardial contraction

- Force increases linearly until a sarcomere length with maximal overlap (2.2 μm) is achieved.
- This is explained by enhanced Ca^{2+} binding to Troponin C, narrower interfilament gaps at long sarcomere length, and increased sarcoplasmic reticulum Ca^{2+} release, uptake at longer sarcomere lengths
- Increased force and overlap gradually decline to zero (descending limb)
- The descending limb of the length–tension relationship is prevented by the strong parallel elastic component in cardiac muscle.

Myocardial contraction

- The relationship between force and velocity of contraction is hyperbolic
- At maximum force (isometric force), shortening cannot occur
- At zero force (ie, unloaded muscle), velocity is at a maximum (V_{max})
- Reflects the maximum turnover rate of myosin ATPase.
- Therefore, alterations in the myosin isoform (α, fast; β, slow) such as those seen in response to pressure overload, have an effect on $V_{max.}$

Myocardial contraction

- Force-plasma Ca^{2+} relation:
- Shorter sarcomere lengths decrease Ca^{2+} sensitivity
- Caffeine and various inotropic drugs are potent Ca^{2+} sensitizers.
- β-Adrenergic stimulation results in a cAMP-dependent phosphorylation of cardiac Troponin I and a resultant decrease in myofilament Ca^{2+} sensitivity
- For a positive β-adrenergic receptor (βAR)–inotropic effect, the amplitude of the Ca^{2+} transient must more than compensate for reduced βAR-mediated myofilament sensitivity.

Myocardial contraction

- Heart rate
- Increasing the heart rate increases contractility
- This is related to the Ca^{2+} capacity and load of the sarcoplasmic reticulum.
- Frequency-dependent acceleration of relaxation
- Results from increased sarcoplasmic reticulum Ca^{2+} transport
- CaMKII phosphorylation of phospholamban

Myocardial contraction

- A fundamental property of striated muscle is that the strength of this isometric twitch is dependent on the initial resting muscle length, or preload
- As cardiac muscle is stretched passively, the resting tension rapidly rises and prevents overstretching of the sarcomeres.
- If additional load is applied before contraction (ie, the preload), stimulation causes contraction with an increased peak tension and rate of tension development (dT/dt).
- Thus, total tension includes both active and passive tension.

Myocardial contraction

- The inotropic state is defined operationally as a change in the rate or extent of force development that occurs independently of the loading conditions
- If isolated cardiac muscle is allowed to shorten, the contraction is termed isotonic
- Initial muscle length is determined by applying a preload; an additional load, known as the afterload, affects muscle behavior after stimulation.
- Muscle shortening occurs when tension development equals the total load (preload plus afterload).
- During shortening, tension remains constant.

Myocardial contraction

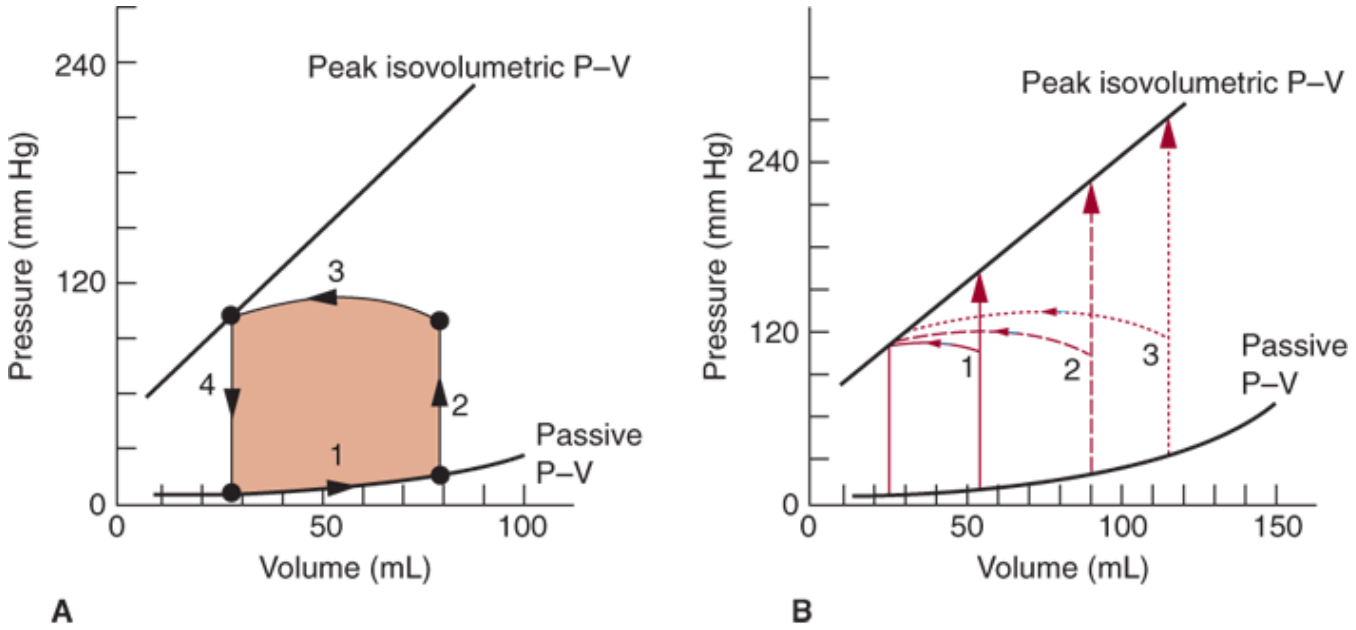
- With dissipation of the active state, the muscle returns to its initial preloaded length, and tension finally declines.
- When the afterload is so great that the muscle cannot shorten, the contraction becomes isometric (P_0).
- The velocity of an unloaded contraction (V_{max}) is considered a measure of the inotropic state.
- The tension at the end of an isotonic contraction is the same as the tension developed from an isometric contraction at the same resting muscle length.

Myocardial contraction

- Contraction of the intact left ventricle is auxotonic
- Force increases and decreases during ejection of viscous blood into a viscoelastic arterial system.
- During ventricular filling, pressure and volume increase nonlinearly (phase I).
- The instantaneous slope of the presure-volume (PV) curve during filling (dP/dV) is diastolic stiffness
- Its inverse (dV/dP) is compliance
- As chamber volume increases, the ventricle becomes stiffer.
- In a normal ventricle, operative compliance is high because the ventricle operates on the flat portion of its diastolic PV curve.

Myocardial contraction

- During isovolumic contraction (phase II), pressure increases and volume remains constant.
- During ejection (phase III), pressure rises and falls until the minimum ventricular size is attained.
- The maximum ratio of pressure to volume (maximal active chamber stiffness or elastance) usually occurs at the end of ejection
- Isovolumic relaxation follows (phase IV)
- When LV pressure falls below left atrial pressure, ventricular filling begins.



A. Left ventricular pressure–volume (P–V) loop, the segments of which correspond to events of the cardiac cycle: diastolic ventricular filling along the passive P–V curve (phase I), isovolumetric contraction (phase II), ventricular ejection (phase III), and isovolumetric relaxation (phase IV). B. The ventricle ejects to an end-systolic volume determined by the peak isovolumetric P–V line; an isovolumetric contraction (large arrowheads) from varying end-diastolic volumes (preload). Reproduced with permission from Sperelakis N, Banks RO: Essentials of Physiology. 2nd ed. Boston: Little, Brown and Company; 1996.

Myocardial contraction

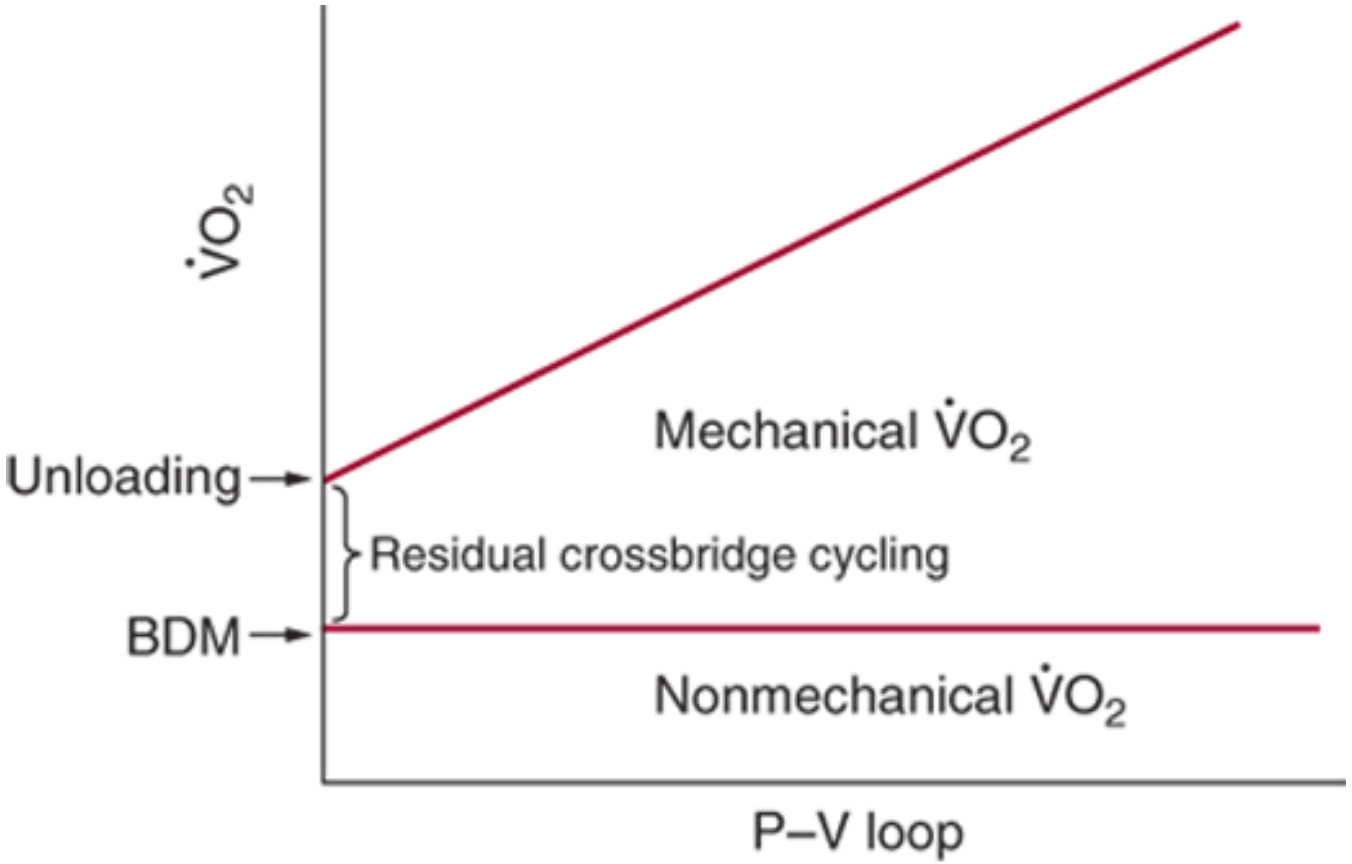
- The PV area (PVA) bounded by the LV PV loop is a measure of the total mechanical energy of LV contraction.
- The total mechanical energy of contraction can be considered to consist of two components:
- (1) external work, the area enclosed within the P–V loop; and
- (2) potential energy stored in the ventricular spring at end systole (ES)

Myocardial contraction

- The VO_2 intercept of the VO_2–PVA relationship is the unloaded VO_2 (PVA–independent VO_2)
- In an isovolumically contracting heart, this corresponds to a point at which LV peak pressure is 0 mm Hg.
- At this point, except for a low level of cross-bridge cycling caused by shape changes, there is neither mechanical energy produced nor energy expended for cross-bridge cycling.

Myocardial contraction

- There is a highly linear correlation ($r > .98$) between LV VO_2/beat and PVA/beat over a wide range of conditions
- The VO_2 under unloaded conditions reflects energy used for electrical-contraction coupling and basal metabolism

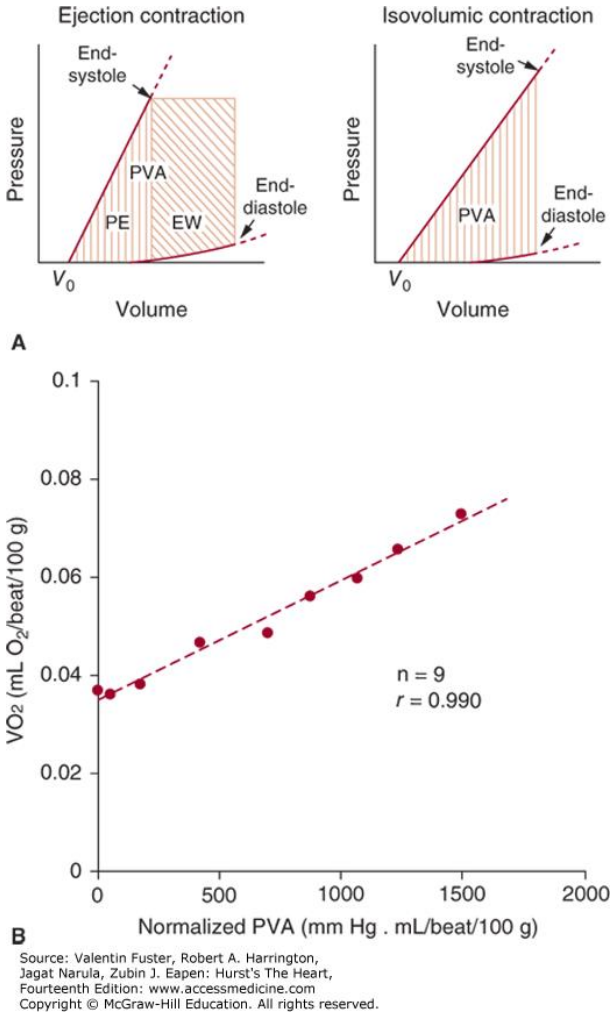


Source: Valentin Fuster, Robert A. Harrington, Jagat Narula, Zubin J. Eapen: Hurst's The Heart, Fourteenth Edition: www.accessmedicine.com

Schematic of the relationship between VO_2/beat and the pressure–volume area (PVA). The diagonal VO_2–PVA line is obtained by mechanical unloading of the ventricle; the y intercept is the unloaded VO_2. Mechanically unloaded VO_2 is subdivided into VO_2 for residual cross-bridge cycling and that for nonmechanical VO_2 (BDM, which inhibits cross-bridge cycling). The latter consists of VO_2 for excitation–contraction (E–C) coupling and basal metabolism. P–V, pressure–volume; VO_2, oxygen consumption. Reproduced with permission from LeWinter MM, Suga H, Watkins MW: Cardiac Energetics: From Emax to Pressure-Volume Area. Norwell: Kluwer Academic Publishers; 1995.

Myocardial contraction

- Oxygen consumption used by the contractile apparatus for cross-bridge cycling is PVA-dependent VO_2
- Increases linearly and directly with PVA.
- PVA-dependent VO_2 is the energy input
- PVA is the total energy output of the contractile machinery
- The inverse slope of the VO_2–PVA relationship is a measure of the thermodynamic efficiency of the contractile machinery.



A. Schematic of the VO_2–PVA (pressure–volume area) concept. In ejecting contractions, PVA = EW + PE; in isovolumic contraction, PVA = PE only. B. Correlation of PVA with VO_2. P–V, pressure– volume; VO_2, oxygen consumption. Reproduced with permission from Fuster V, Alexander RW, O'Rourke RA, et al: Hurst's The Heart. 11th ed. New York: McGraw-Hill; 2004.

Myocardial contraction

- Cardiac output responds to changes in the oxygen requirements of tissues
- The stroke volume expressed as a function of the end-diastolic volume is the ejection fraction (EF). Thus, EF = (End-diastolic volume – End-systolic volume)/End-diastolic volume.
- Stroke work (the product of pressure and stroke volume) equals the area bounded by the ventricular PVA
- ([Mean LV systolic – Diastolic pressure] × Stroke volume × 0.0136)

Myocardial contraction

- The modulation of ventricular performance by changes in preload (heterometric regulation) operates on a beat-by-beat basis and is responsible for matching outputs of the RV and LV, as with changes in posture and breathing.
- The Frank-Starling curve also represents an important compensatory mechanism that maintains LV stroke volume in relation to increasing LV end-diastolic volume when LV shortening is impaired
- Examples are myocardial contractile dysfunction or excessive afterload.
- The atria also exhibit a Frank-Starling curve

Myocardial contraction

- The passive PV relationship is not linear but exponential.
- The ratio of change in LV pressure to volume is greater at higher than at lower LV volumes.
- Chronic volume overload can shift the ventricular diastolic pressure relationship so that volume is increased at a normal end-diastolic pressure
- Chronic pressure overload can shift the diastolic P–V relationship and for the same end-diastolic pressure result in a smaller ventricular volume
- Ultrasound determination is best clinical approach for pressures and volumes

Myocardial contraction

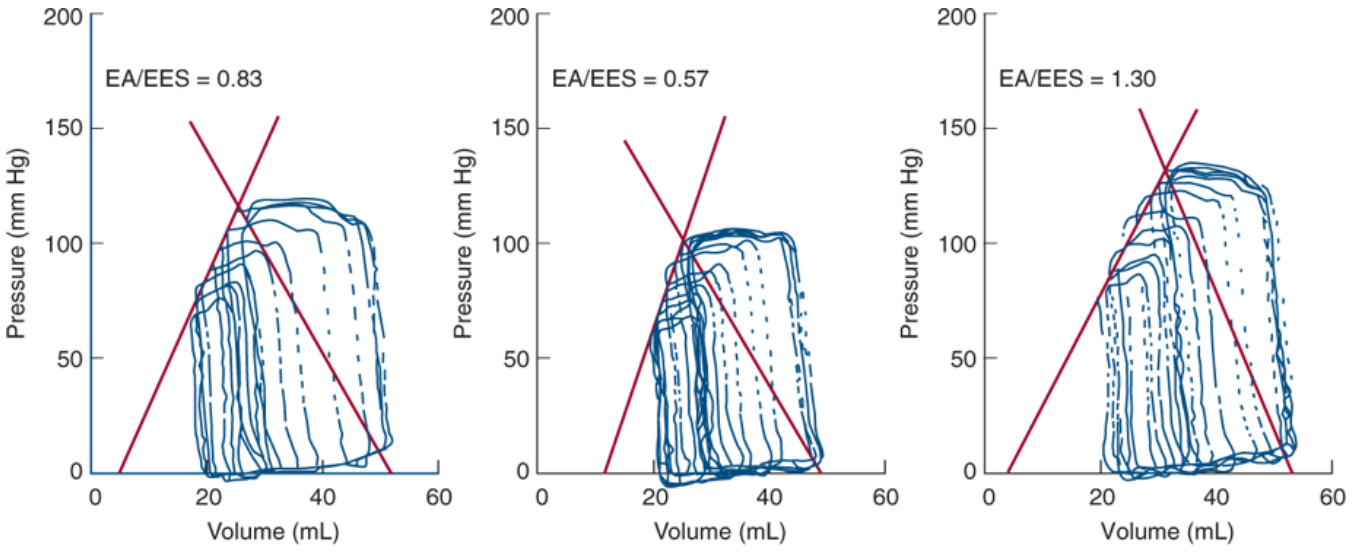
- Afterload in the intact heart can be considered as the tension in the LV wall that resists ventricular ejection (wall stress during systole)
- OR as the arterial input impedance (the ratio of instantaneous change in pressure to instantaneous change in flow).
- Systolic wall stress can be derived from application of the Laplace relationship
- Wall tension (τ) = $(P \cdot r)/2\ h$, where P refers to pressure, r to ventricular radius, and h to wall thickness.

Myocardial contraction

- More complex derivations based on various geometric assumptions are used to calculate end-systolic wall stress.
- Input impedance is a complex function of arterial pressures, elasticity, vessel dimension, and blood viscosity.
- Arterial pressure is the surrogate measure for afterload.
- An increase in afterload causes a decrease in stroke volume and the velocity of LV shortening.

Myocardial contraction

- End-systole (ES) can be defined as end ejection or as the time of maximal elastance (the maximal PV ratio) during systole.
- Preload recruitable stroke work (slope of the end-diastolic volume–stroke work relationship) and the slope of the end-diastolic volume–dP/dtmax relationship are linear and afterload independent.
- Preload recruitable stroke work is independent of heart size
- The slope of the EDV–dP/dtmax is sensitive to an inotropic state



Ventriculoarterial coupling using the arterial elastance-LV end-systolic relation (EA/EES). A. Baseline. B. Nitroprusside increases EES with little change in EA, resulting in a decrease in EA/EES. C. Angiotensin II increases EA without a change in EES, resulting in an increase in EA/EES. LV, left ventricular. Reproduced with permission from LeWinter MM, Suga H, Watkins MW: Cardiac Energetics: From Emax to Pressure-Volume Area. Norwell: Kluwer Academic Publishers; 1995.

Myocardial contraction

- $\ln P = -1/T + \ln P_0$.
- The relaxation time constant, T, is derived by obtaining the negative of the reciprocal of the slope of lnP (pressure at any time) versus time, t, from aortic valve closure to mitral valve opening (isovolumic relaxation).
- P_0 is the pressure at the beginning of LV relaxation
- T is less load dependent measure of contraction

Myocardial contraction

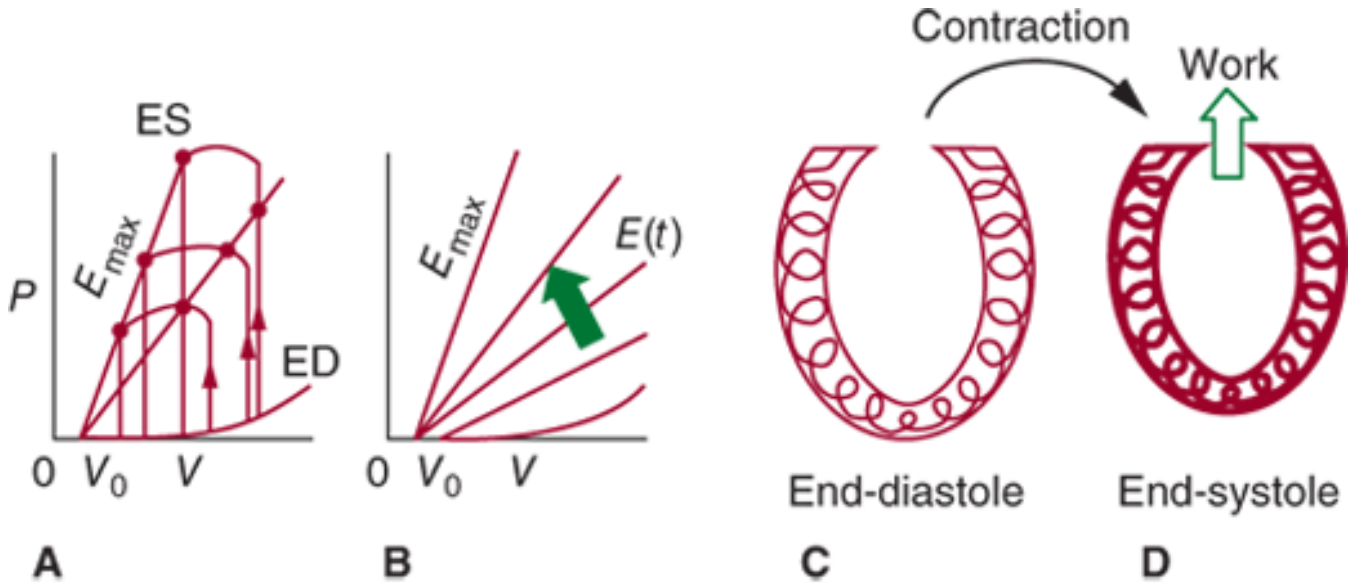
- In addition to relaxation, the passive viscoelasticity of the ventricle is dependent both on intracellular and extracellular structures
- It is a major determinant of diastolic function
- The P–V relationship during early diastole reflects the lusitropic (relaxation) state of the heart, analogous to the inotropic (contraction) state measured during systole.
- The rate of LV relaxation can be estimated from the maximal rate of pressure decay (–dP/dtmax)

Myocardial contraction

- Diastole occurs in a series of energy-consuming steps:
- Release of Ca^{2+} from Troponin C
- Detachment of actin–myosin cross-bridges
- SERCA2a-induced Ca^{2+} sequestration into the sarcoplasmic reticulum
- NCX-induced extrusion of Ca^{2+} from the cytoplasm
- Return of the sarcomere to its resting length.
- Adequate ATP must be present for these processes to occur at a sufficient rate and extent.

Myocardial contraction

- During contraction, cytoskeletal proteins such as titin and microtubules are deformed by actin–myosin cross-bridge cycling and sarcomere contraction, which act like viscoelastic springs during diastole.
- This reclaimed potential energy constitutes a recoiling force that helps restore the myocardium to its resting configuration.
- In addition, extracellular matrix proteins such as collagen contribute to the establishment of resting force and length.



The time-varying elastance concept. A. A series of variably loaded pressure–volume areas (PVAs). The relationship between pressure and volume at any time, t, during variably loaded contractions under constant contractility conditions is linear and reaches a maximum value at end-systole (ES). Filled circles connected by straight lines occur at the same time, t, during contraction. E_{max} is the line connecting the points at ES. B. Elastance, E (t) increases at each time, t, during contraction until it reaches maximal values at ES. Increasing contractility increases the slope at any time, t, including ES (E_{max}). C,D. The concept that the ventricle behaves as an elastic spring with a stiffness (elastance) that increases during systole and decreases during diastole (EES or E_{max}). D, diastole; ED, end-diastole; P, pressure; S, systole; V, volume; V_0, dead volume. Reproduced with permission from Fuster V, Alexander RW, O'Rourke RA, et al: Hurst's The Heart. 11th ed. New York: McGraw-Hill; 2004.

Myocardial contraction

- Operating stiffness changes throughout filling
- Stiffness (dP/dV) is less at smaller volumes and greater at larger volumes.
- Because the diastolic PV relationship is generally exponential, the relationship between dP/dV and pressure is linear.
- The slope of this relationship is called the modulus of chamber stiffness (kc) and has been used to quantitate chamber stiffness.

Myocardial contraction

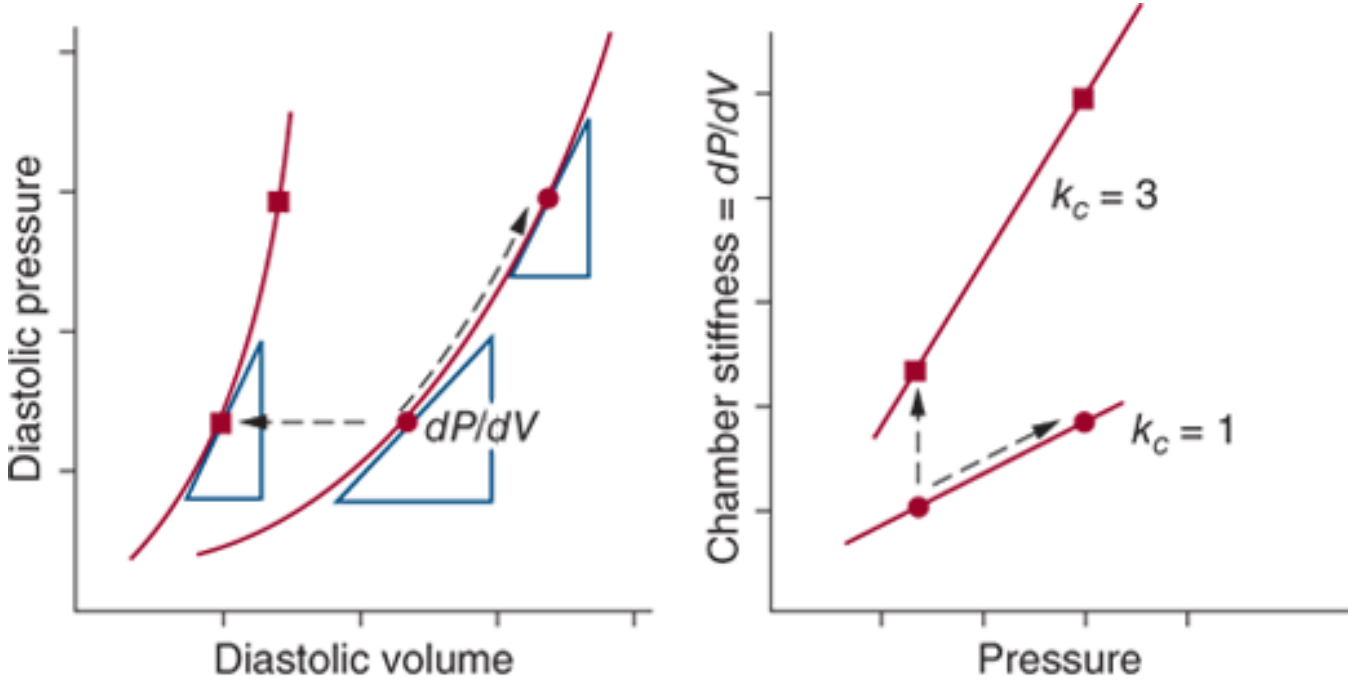
- When chamber stiffness is increased, the P–V curve shifts to the left, the slope of the dP/dt versus pressure relationship becomes steeper, and kc is increased.
- Myocardial stiffness is quantified from the relationship between diastolic LV wall stress (ε) and strain (σ).

Myocardial contraction

- Strain is the deformation of the muscle produced by an applied force and is expressed as the percent change in length from the unstressed length.
- At any given strain throughout diastole, myocardial stiffness is equal to the slope ($d\sigma/d\varepsilon$) of a tangent drawn to the stress–strain curve at that strain.
- Because the stress–strain relationship is generally exponential, the relationship between ($d\sigma/d\varepsilon$) and stress is linear.

Myocardial contraction

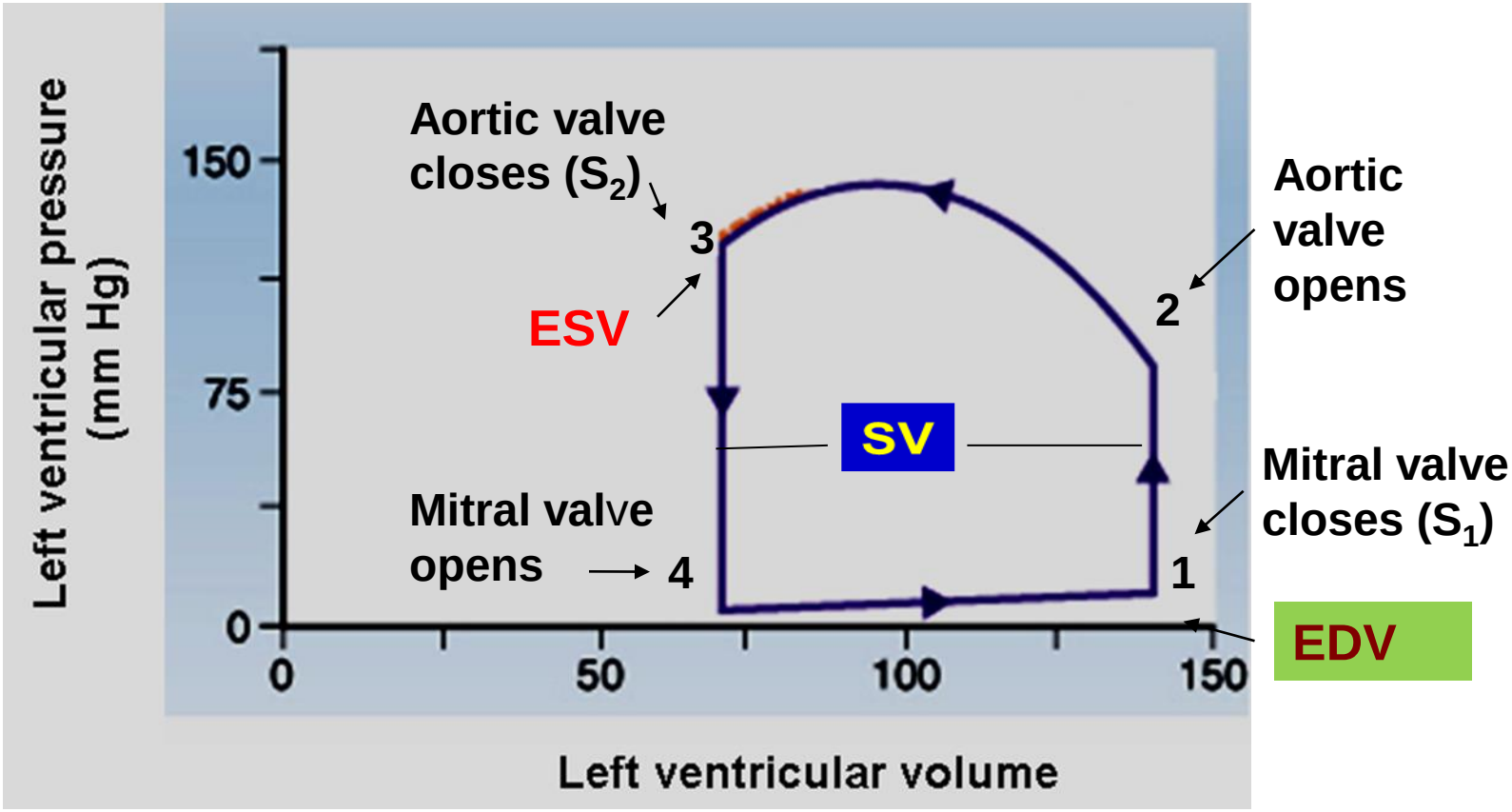
- The slope of this relationship is the modulus of myocardial stiffness (Km) and has been used to quantitate myocardial stiffness.
- When myocardial stiffness is increased the slope of the ($d\sigma/d\varepsilon$) versus stress relationship becomes steeper, and Km increases.



A. End-diastolic pressure–volume relationship (EDPVR) in two ventricles with differing passive diastolic properties. Chamber stiffness is dP/dV at any point on the EDPVR. The stiffer chamber on the left has a steeper overall slope. B. The same data plotted as pressure versus chamber stiffness. Because of the exponential nature of EDPVR, the relation between chamber stiffness and pressure is a straight line whose slope is the chamber stiffness constant (k_c) that characterizes the overall slope of the EDPVR. A similar relationship holds for stress and strain. Reproduced with permission from Fuster V, Alexander RW, O'Rourke RA, et al: Hurst's The Heart. 11th ed. New York: McGraw-Hill; 2004.

Left ventricular pressure-volume loop

1 to 2 : Isovolumetric ventricular contraction
2 to 3 : Left ventricular ejection
3 to 4 : Isovolumetric ventricular relaxation
4 to 1 : Left ventricular filling



Left ventricle dynamics

- In the left ventricle myocardial wall, the geometry of the myofibers changes smoothly from a right-handed helix in the subendocardium to a left-handed helix in the subepicardium.
- The helix angle varies continuously from positive at the endocardium to negative at the epicardium.
- When both layers contract simultaneously, a larger radius of rotation for the outer epicardial layer results in epicardial fibers having a mechanical advantage (torque) in dominating the overall direction of rotation.

Left ventricle dynamics

- The large subepicardial torque is coupled transmurally to the midwall and subendocardium.
- Results in a global counterclockwise left ventricle rotation near the apex and clockwise rotation near the left ventricle base during ejection.
- In the subepicardium, this twist aids contraction in the principal fiber direction.
- In the midwall, this torque enhances shortening in the circumferential direction.

Left ventricle dynamics

- In the subendocardium, this torque causes
- Fiber rearrangement such that subendocardial fibers are sheared toward the left ventricle cavity for left ventricle wall thickening,
- While the left ventricular base is pulled toward the apex, shortening the longitudinal axis of the left ventricle.
- Results in storage of potential energy, which is subsequently utilized for diastolic recoil

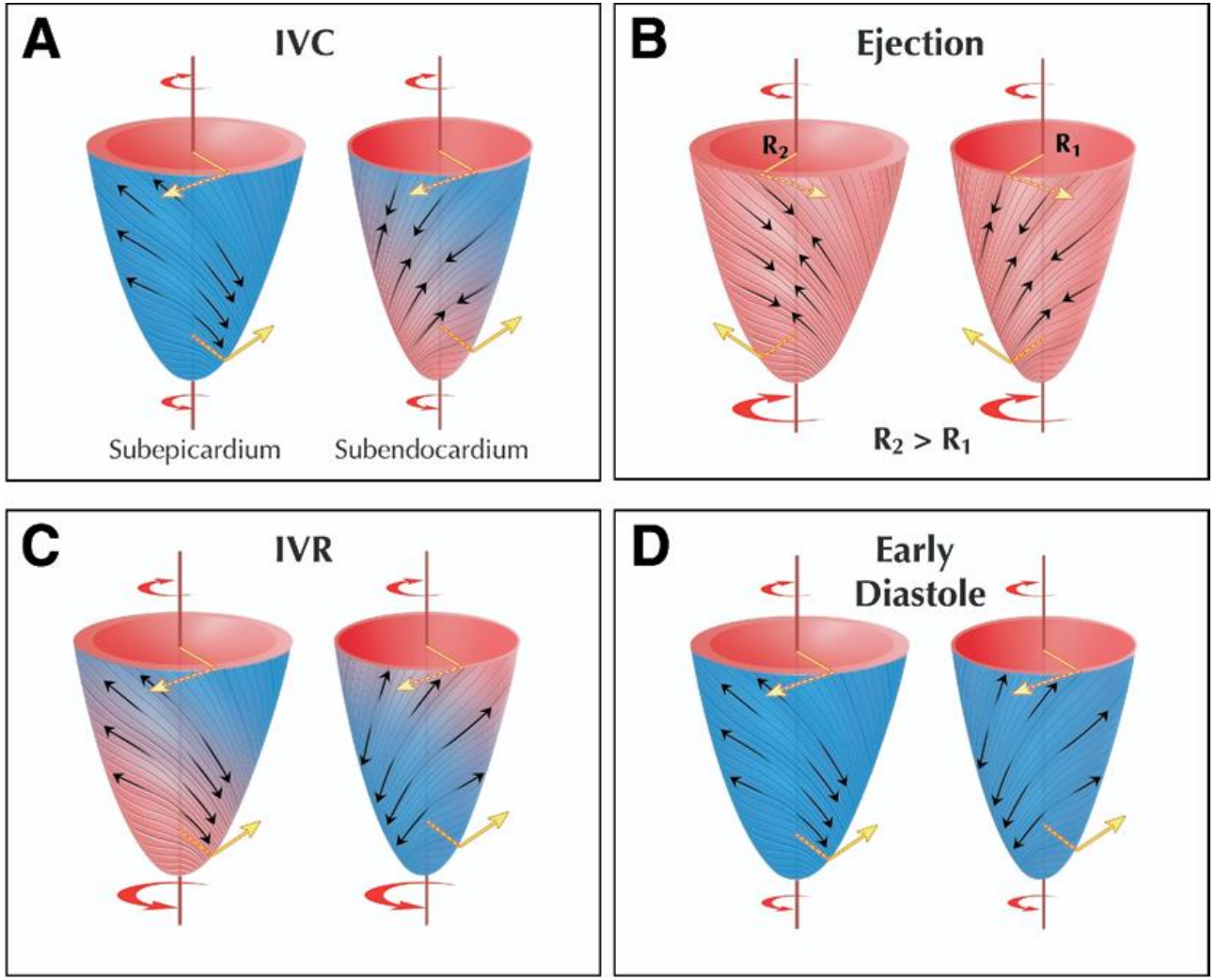
Left ventricle dynamics

- The torsional recoil during isovolumic relaxation and early diastole releases the potential energy stored in the deformed matrix of the subendocardium.
- This process is facilitated by presence of lengthening-shortening gradients in the left ventricle wall, which hasten lengthening of relaxed segments.
- Torsion helps bring a uniform distribution of left ventricle fiber stress and fiber shortening across the wall.
- In the normal heart both the right ventricle and the left ventricle are coupled for twisting in the same direction.

Left Ventricle

- The functional consequence of this three-dimensional helical structure is a cyclic systolic twisting deformation, resulting from clockwise basal rotation and counterclockwise apical rotation (as seen from the apex).
- Makes it possible that only 15% fiber shortening results in a 60% reduction in left ventricular volume.

Left ventricle dynamics



Sengupta, Partho P, Tajik, J,Chandrasekaran, Krishnaswarmy, Khandheria, Bijoy K, “Twist Mechanics of the Left Ventricle:
Principles and Application”
Journal of Clinical Cardiology: Cardiovascular Imaging (2008) 1: 366-375.
D O I : 1 0 . 1 0 1 6 / j . j c m g . 2 0 0 8 . 0 2 . 0 0 6

Accessed 01/20/2020

Left ventricle dynamics

- Elimination of the torsion would decrease epicardial shortening and increase endocardial shortening.
- Increase endocardial stress and strain
- Increase Oxygen demand
- Reduce the efficiency of left ventricle systolic function.

Left ventricle dynamics

- The left ventricle twists increase gradually from infancy to adulthood.
- Attributed to the maturation of the helical myofiber architecture of the left ventricle wall
- Counterclockwise apical rotation is constant in its magnitude during childhood
- The basal rotation changes:
- Initially counterclockwise in infancy to neutral in early childhood
- The adult clockwise pattern in adolescence.

Left ventricle dynamics

- With increasing age, subendocardial function may gradually attenuate, and LV twist increases further because of an unopposed increase in left ventricle apical rotation
- Age-related degenerative changes reduce the elastic resilience of the myocardial wall, and therefore the velocity of untwisting in early diastole reduces progressively.
- Associated with reduced torsional reserves at peak exercise.

Left ventricle dynamics

- Left ventricle systolic twisting and untwisting can almost double with short-term exercise because of augmented rotation of both apical and basal levels.
- Store additional potential energy that is released for improving diastolic suction.
- Left ventricle twist is reduced with exercise training and may represent increased torsional reserves that are used in increased-demand situations such as high-intensity sports.

Left ventricle dynamics (Summary)

- Alterations in fiber-orientation influence left ventricular peak systolic twist.
- The curvature of the left ventricular wall is related to wall tension.
- Deformation of myocardial fibers is known to be inversely related to wall tension.
- Changes in cardiac shape may also lead to changes in left ventricular twist by means of alterations in wall tension

Left ventricle dynamics (summary)

- Afterload increases twisting action as it leads to increased endocardial wall tension.
- Preload effect two-thirds that of afterload.
- There is a direct inotropic effect on twist not effected by volume but by changes in force.
- Diastolic untwisting of the left ventricle plays a crucial role in diastolic suction.
- This may be caused by a temporal dispersion between basal and apical de-rotation, the diastolic reversal of systolic rotation.

Left ventricle dynamics Pathologic states

- Left ventricle twist may remain preserved in patients with diastolic dysfunction in presence of normal ejection fraction.
- Left ventricle twisting and untwisting rates are reduced in patients with left ventricle systolic dysfunction and depressed ejection fraction.
- Early diastolic left ventricle untwisting and untwisting rates are significantly delayed and reduced in parallel to the severity of left ventricle hypertrophy.

Left ventricle dynamics Pathologic states

- There is greater-than-normal apical rotation with subendocardial ischemia
- There is less-than-normal apical rotation with transmural ischemia.
- In aortic valve stenosis, coronary flow diminishes in the subendocardial region relative to the subepicardial region.
- The left ventricle twist is significantly increased, and diastolic apical untwisting is prolonged.
- The delay in apical untwisting is associated with diastolic dysfunction and elevated LVEDP.

Left ventricle dynamics Pathologic states

- Long standing mitral regurgitation reduces systolic left ventricle twist because of a decreased leverage of the epicardial fibers relative to the endocardial muscle fibers.
- Although increased preload will tend to increase systolic twist , mitral regurgitation is associated with complex left ventricle adaptive remodeling and eccentric hypertrophy.
- Loss of left ventricle torsional mechanics in remodeled hearts may be difficult to restore once already established.

Left ventricle dynamics
Pathologic states

- In dilated cardiomyopathy, amplitude of peak LV systolic twist is impaired in proportion to the global left ventricle function.
- Marked attenuation of left ventricle apical rotation.
- Basal rotation may be spared.

Left ventricle dynamics Pathologic states

- In hypertrophic cardiomyopathy left ventricle net twist is preserved, although the apex-to base progression of the twist sequence is altered.
- Rotation at the mid-LV level becomes clockwise, similar to the direction of rotation of the LV base (opposite to normal) The area where rotation crosses over from clockwise into a counterclockwise direction, is apically displaced.

Left ventricle dynamics Pathologic states

- This causes regional heterogeneity of LV twist, reducing the gradient of LV rotation for the basal aspect of LV, while exaggerating it toward the LV apex.
- Lower untwisting velocities marked with exercise in hypertrophic cardiomyopathy.

Left ventricle in the young

- There is a marked contribution of active left ventricular relaxation to left ventricular filling.
- Accentuates early diastolic filling velocity with a short deceleration time, resembling restrictive left ventricular filling.
- Very rapid left ventricular untwisting plays a pivotal role in this physiological rapid early diastolic filling.
- In dilated cardiomyopathy, in contrast, untwisting is delayed and impairs left ventricular filling through loss of suction.

Left ventricle in aging

- The increase of left ventricular twist with aging results not only from an increase in apical peak systolic rotation but also from a decrease in rotational deformation delay.
- Loss of the opposed action of subendocardial fibers allows the subepicardial fibers to cause more pronounced left ventricular apical rotation, and, left ventricular twist.

Left ventricle in aging

- Left ventricular twist increases
- Time-to-peak left ventricular basal rotation remains relatively unchanged
- Left ventricular apical peak rotation occurs later in systole, approaching time-to-peak basal rotation
- Decrease rotational deformation delay
- Subendocardial dysfunction leading to loss of the counteraction to the subendocardial fiber helix.
- May reflect prolonged contraction.

Left ventricle in aging

- The early diastolic release of increased potential energy stored during this augmented systolic twisting deformation may be the cause of preserved peak diastolic untwisting velocity and untwisting rate with aging.
- Both parameters are significantly impaired when normalized for the increased extent of left ventricular twist.
- This results in a progressive delay in relative left ventricular untwisting and in the time-to-peak diastolic untwisting velocity with aging (stiffness).

Left ventricle in aging

- The same subendocardial dysfunction that is supposed to lead to increased left ventricular twist with aging, may also lead to loss of the active part of untwisting normally caused in early diastole by still depolarized subendocardial fibers.
- Relatively reduced and delayed left ventricular untwisting may help to explain the increased duration of isovolumic relaxation in the elderly.

Left ventricle in aging

- Because left ventricular untwisting generates the left ventricular pressure gradient that helps filling the left ventricle, impediment of left ventricular untwisting leads to delayed generation of this pressure gradient, and to delayed opening of the mitral valve.
- In women, there is a second complication, as the pumping mechanism of the soleus is impaired.

Left ventricle in diabetes mellitus

- Increased left ventricular twist is also described in diabetics with a normal left ventricular ejection fraction.
- Potential mechanisms for the loss of counteraction of the subendocardial fibers include:
- Metabolic disturbances triggered by hyperglycemia
- Increased free fatty acid oxidation
- Altered calcium homeostasis
- Myocyte death and fibrosis
- Small-vessel diseases
- Cardiac autonomic neuropathy.

Left ventricle resynchronized

- One, subepicardial left ventricular twist reflects the positive effects of cardiac resynchronization therapy better than subendocardial left ventricular twist, as the subepicardial layer is the major determinant of left ventricular twist.
- Two, left ventricular pacing in cardiac resynchronization therapy is applied from the epicardial surface, which may be more closely related to mechanical changes in the subepicardial than the subendocardial left ventricular layer.

Left ventricle in aortic stenosis

- Aortic stenosis patients are consistently found to have increased left ventricular twist, mainly due to increased left ventricular apical rotation.
- Increased afterload leads to increased endocardial wall tension and decreases endocardial deformation.
- Left ventricular apical rotation and twist are highest in those patients with symptoms (angina) or electrocardiographic signs (strain) compatible with subendocardial ischemia.

Left ventricle in failure

- Immediate improvement of subepicardial left ventricular twist is independently related to favorable outcomes and has incremental value over established parameters.

Isometric contraction

- Following atrial systole, the left ventricle fills (diastolic suction).
- The muscle force builds up to reach the afterload.
- Myocardial fiber length increases
- Overlap of thick and thin filaments
- Cross-bridge
- ATP hydrolyzed as energy source

Isotonic shortening

- Once the after-loaded muscle generates enough tension to equal the total load, it will then shorten isotonically because its contractile potential still exceeds its tension output
- In the normal heart at the peak of the shortening, the after-load is removed because of the closing of the aortic and pulmonary valves at the end of the cardiac ejection phase (ventricular systole).
- During isotonic shortening, the muscle force is limited by the magnitude of the after-load and not by the length-tension capability of the muscle.

Isotonic shortening

- Rotation of the left ventricle apex reverses rapidly and becomes counterclockwise during left ventricle ejection
- The work done on the load is not returned to the muscle but is imparted to the after-load (ejected blood).
- Although late in systole aortic pressure does exceed left ventricular pressure, momentum of ejected blood keeps it flowing out of the left ventricle
- Pressure relations in the right ventricle and pulmonary artery are similar.

Isometric relaxation

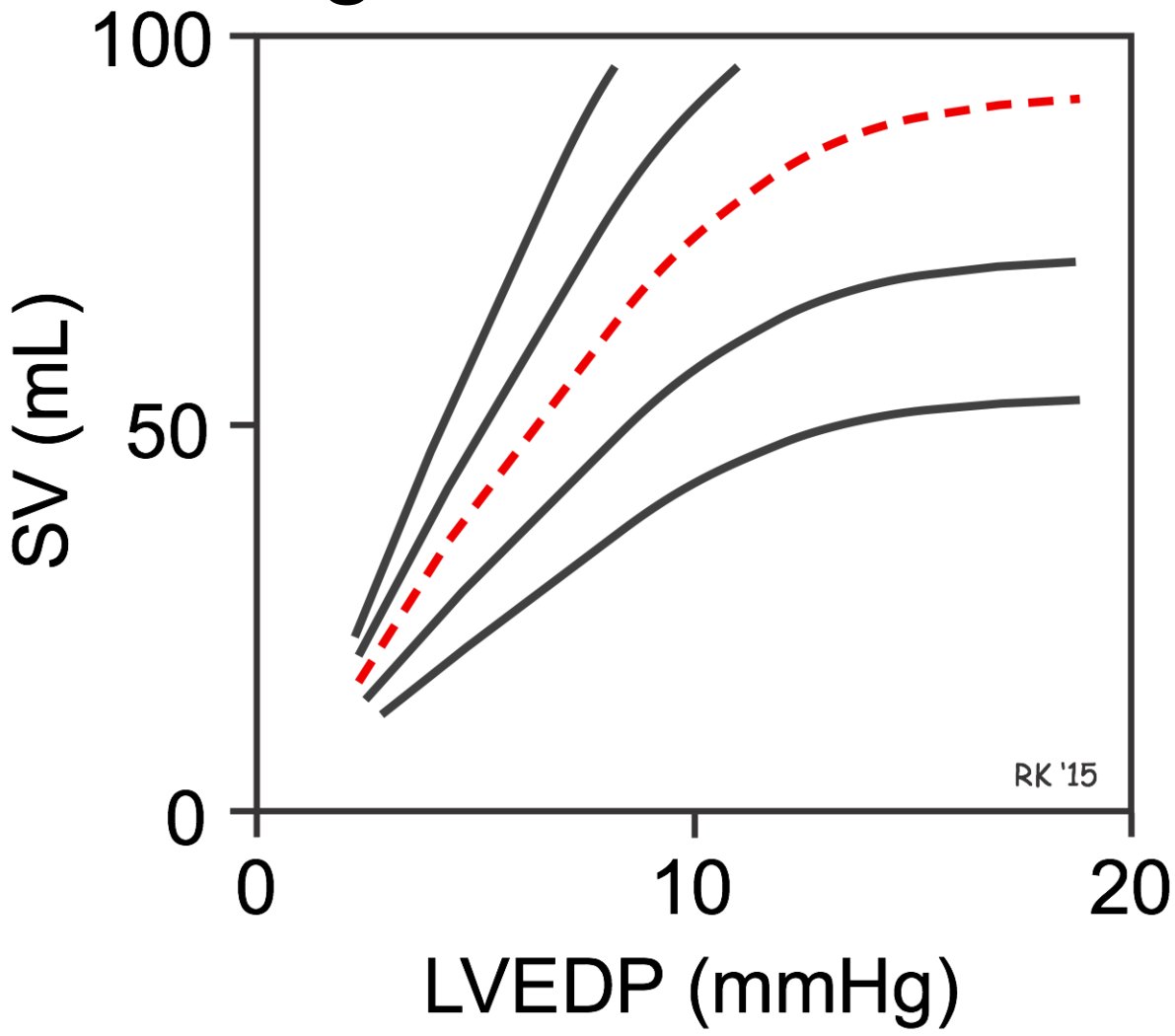
- The force dies away.
- As the muscle is not allowed to lengthen (the inflow valves are still closed), it undergoes isometric relaxation at the shorter length.
- In the normal resting heart about 40% of left ventricular untwisting occurs during isovolumic relaxation.
- Proportional to the rate of isovolumic pressure decay.
- In addition, left ventricular untwisting precedes and is a strong predictor of the intraventricular pressure gradient, a marker of diastolic suction during early left ventricular filling.

Isotonic lengthening

- The preload stretches the muscle back to its starting length by the force of the returning blood
- Because the muscle has relaxed, only a small force is required for the re-extension.
- In the intact heart, this force is supplied by the returning blood.

Frank-Starling mechanism

- The normal heart can change its force of contraction and, therefore, stroke volume to changes in venous return
- The result is enhanced contractility and increased stroke volume



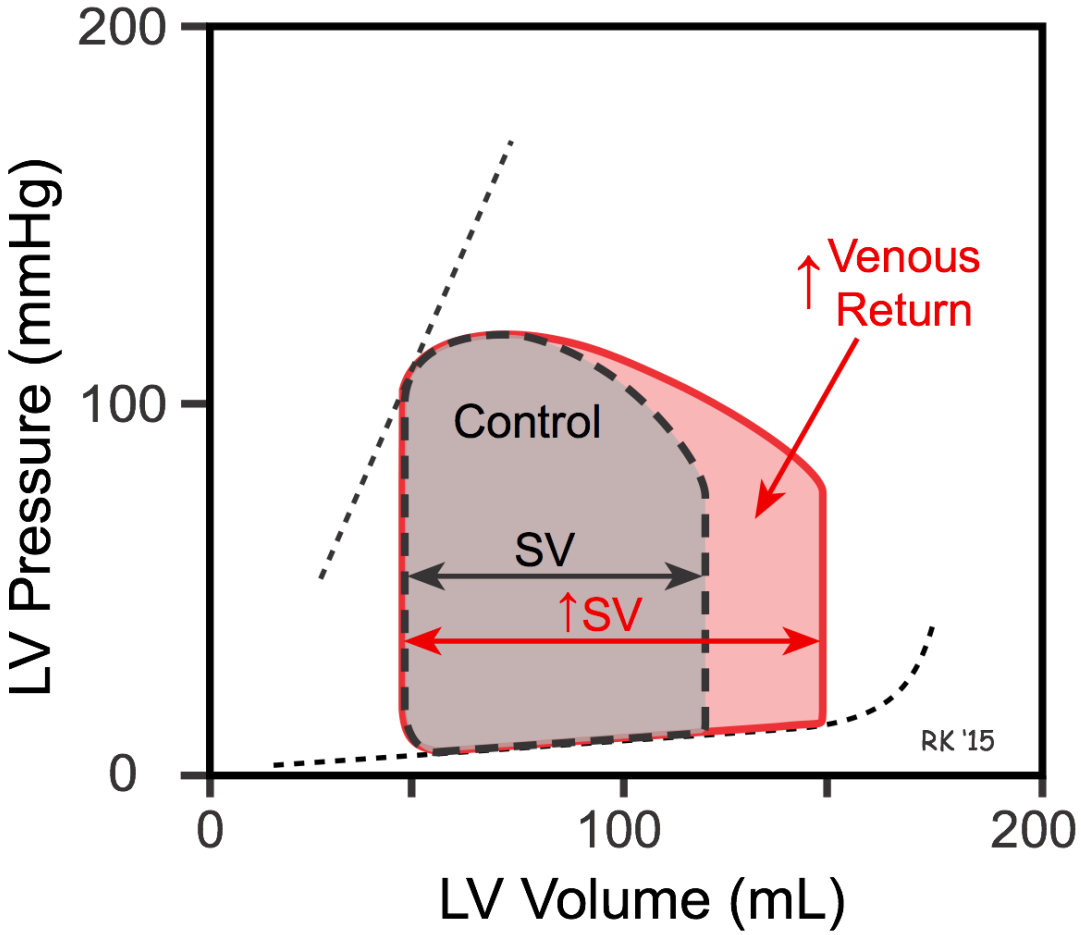
https://www.cvphysiology.com/Cardiac%20Function/CF003
Accessed 12/10/2019

Frank-Starling mechanism

- Increased preload in the normal heart leads to stretching of the myocyte (sarcomere)
- End-diastolic volume increases while pressure is held constant
- Increasing the sarcomere length increases the calcium sensitivity of Troponin C
- The rate of cross-bridge attachment and detachment increases
- The amount of tension developed by the muscle fiber increases

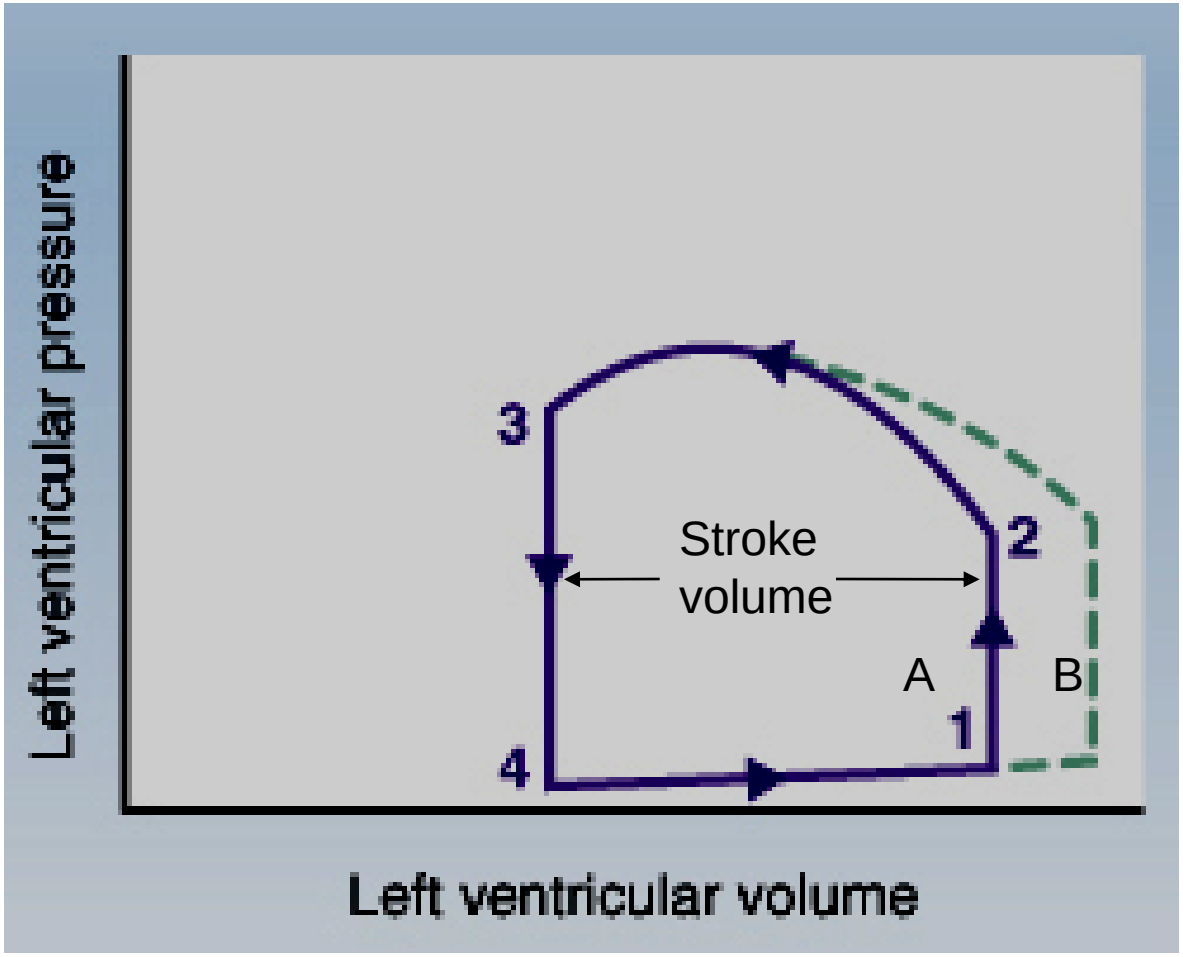
How stroke volume increases

If the ventricle now contracts at this increased preload, without change in the afterload and inotropy, the ventricle empties to the same end-systolic volume (increase in the width of the pressure-volume loop).



https://www.cvphysiology.com/Cardiac%20Function/CF003
Accessed 12/10/2019

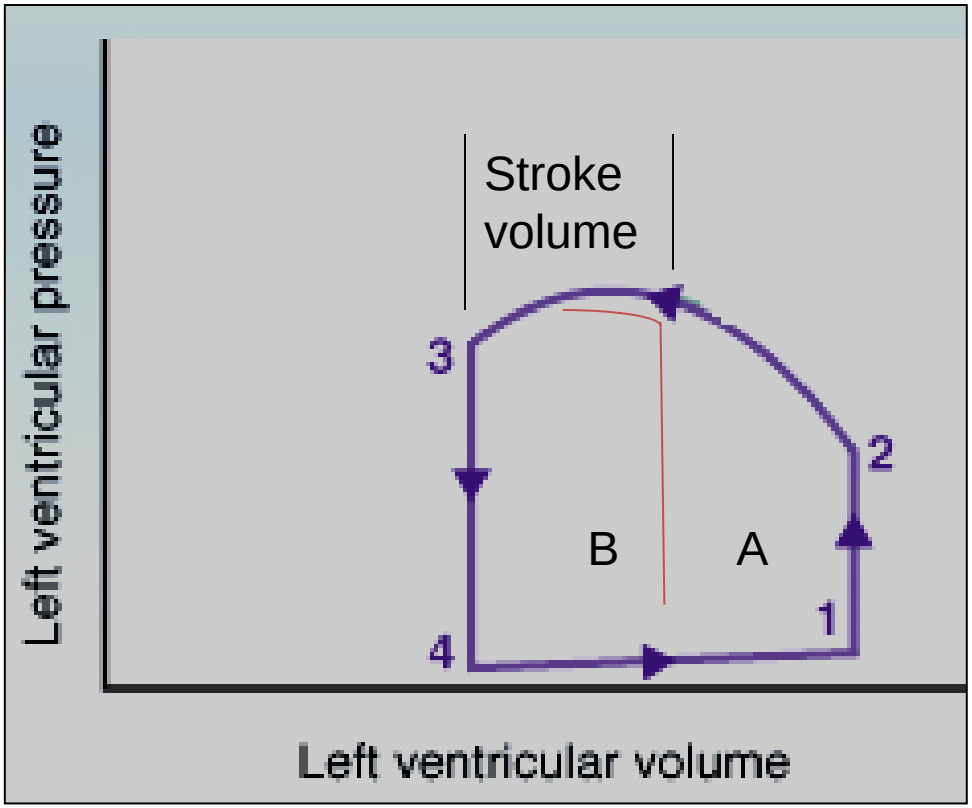
Increase in preload



A. Normal heart
B. Increased preload

EDV increases

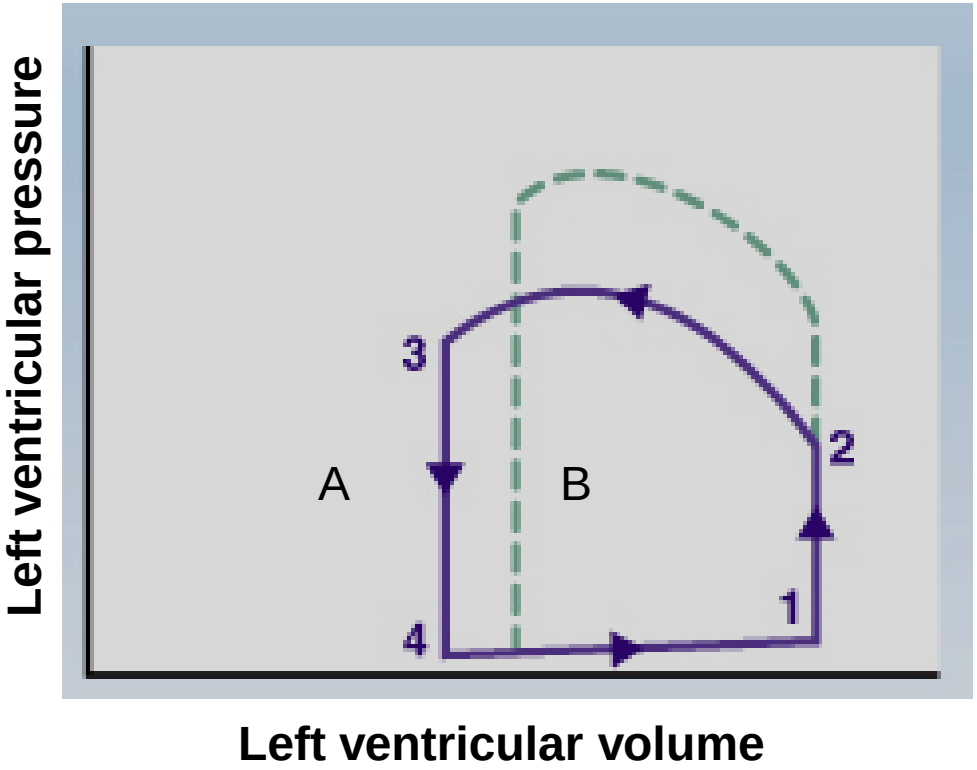
Decrease in preload



A. Normal heart
B. Decreased preload

EDV decreases

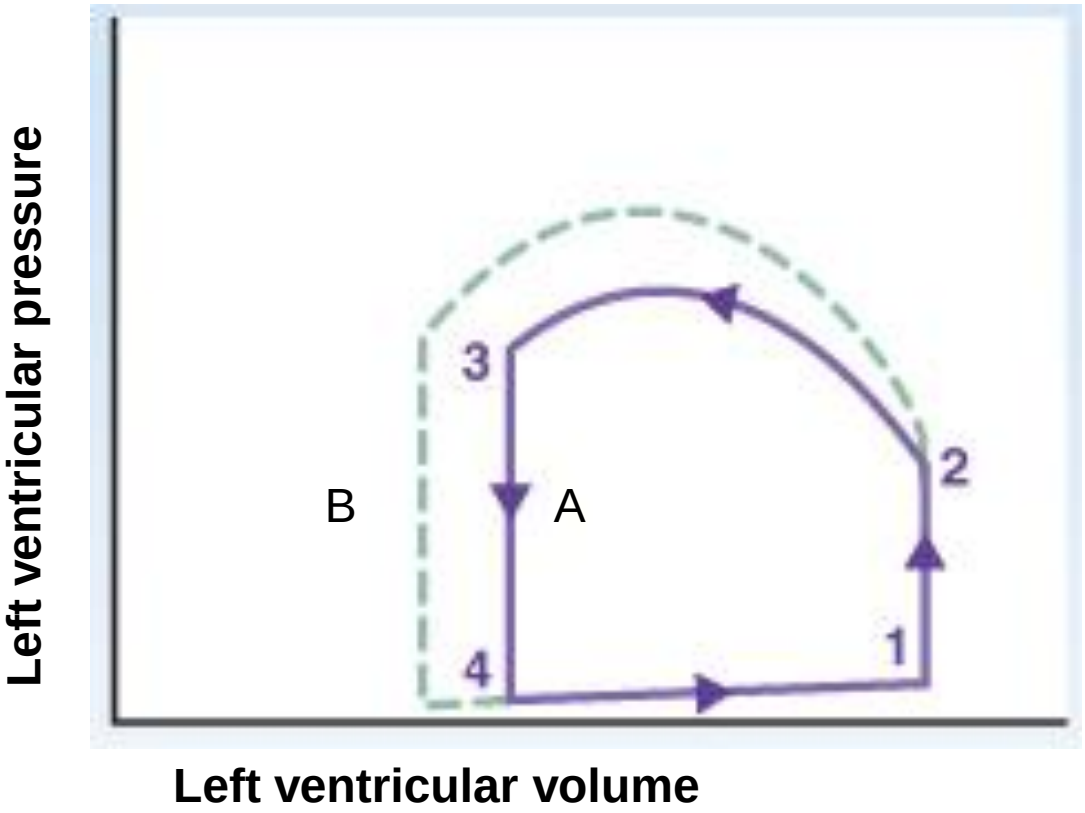
Increase in afterload



A. Normal
B. Increased afterload

1. Increased systolic pressure
2. Decreased stroke volume
3. Increased end systolic volume

Increased myocardial contractility



A. Normal
B. Increased contractility

1. Increased systolic pressure
2. Increased stroke volume
3. Increased ejection fraction
4. Decreased end systolic volume

Increased contractility and end systolic pressure volume

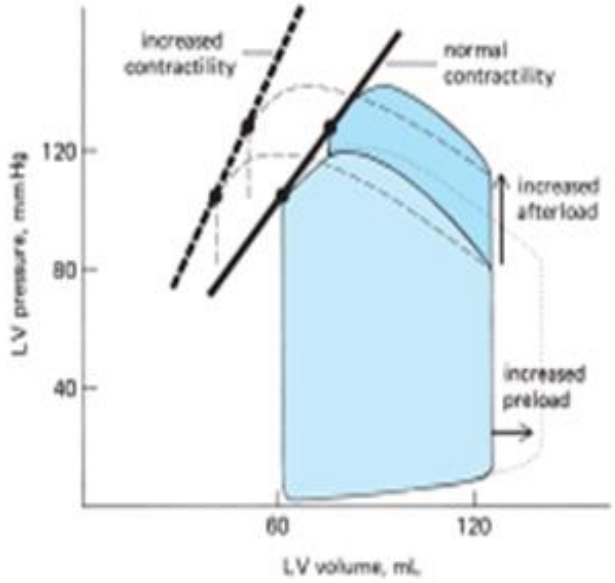
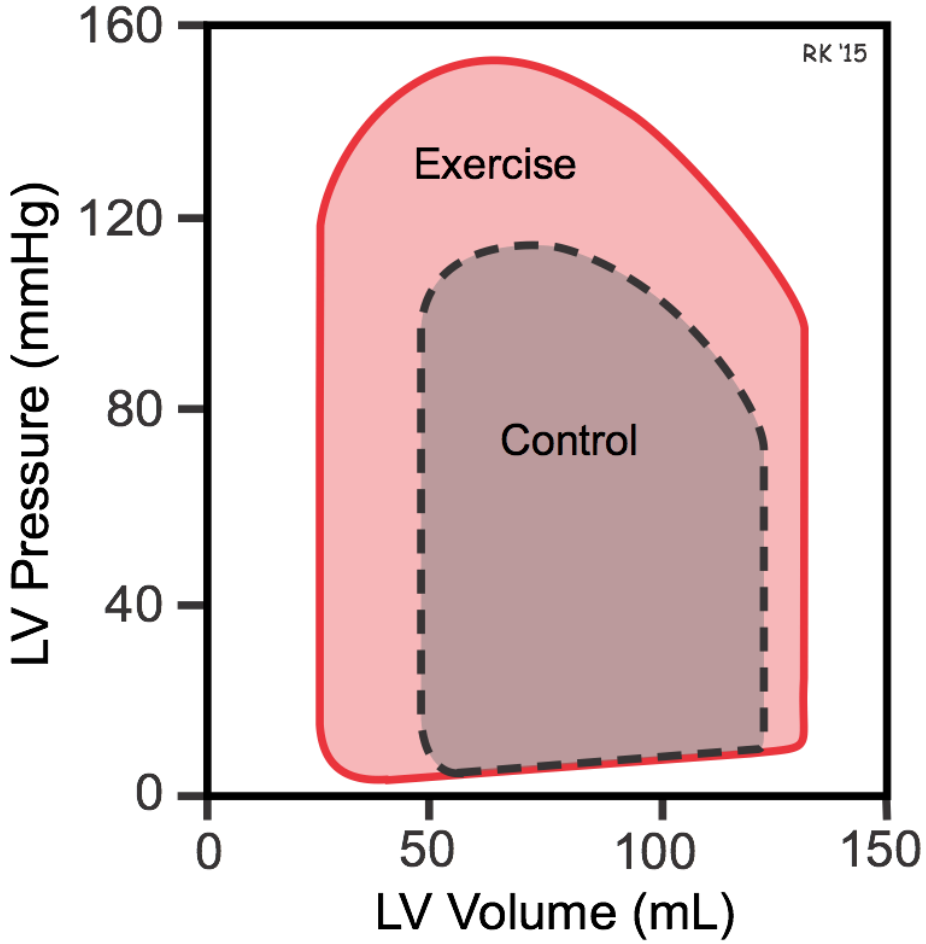


Fig. 3-9 Accessed 32/01/2010

Only alterations in contractility will cause shifts in the end-systolic pressure-volume relationship.

P-V LOOP IN SEVERE EXERCISE



Summary of events

- The initial velocity of shortening (ejection) is maximal at zero after-load.
- At maximum after-load, velocity is zero (isometric).
- For a given afterload, initial velocity of shortening is higher with increased preload or increased contractility.
- Stroke volume increases.
- With increased venous return (preload), end diastolic volume (EDV) increases.

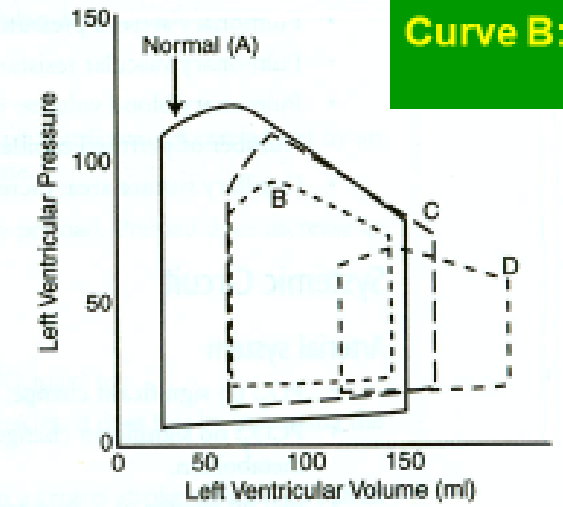
Cardiac function curves in heart failure

- With a reduction in contractility, the cardiac output falls
- Blood volume expansion partially restores cardiac output by Frank-Starling mechanism.
- Gradually progresses to massive volume expansion.
- As heart failure progresses, there is a severe reduction of contractility due to overstretching of ventricular myocardial musculature with loss of tension (Laplace Law).
- The ventricle decompensates.

P-V loop in Left ventricular failure

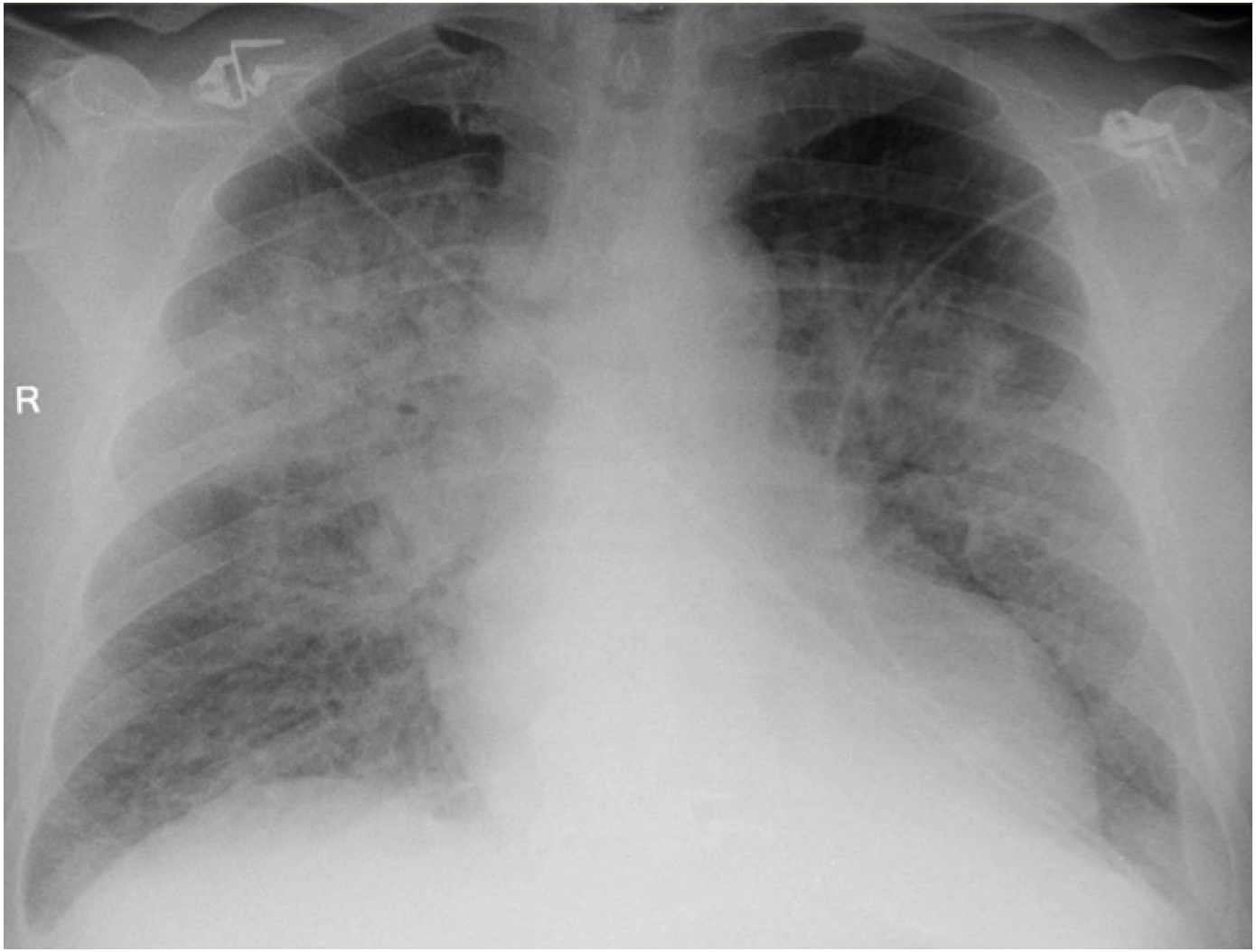
Curve A: Normal

Curve B: Immediate effect of reduced contractility – no compensation



Curve C: Compensated LV failure - SV is partially restored due to increased preload

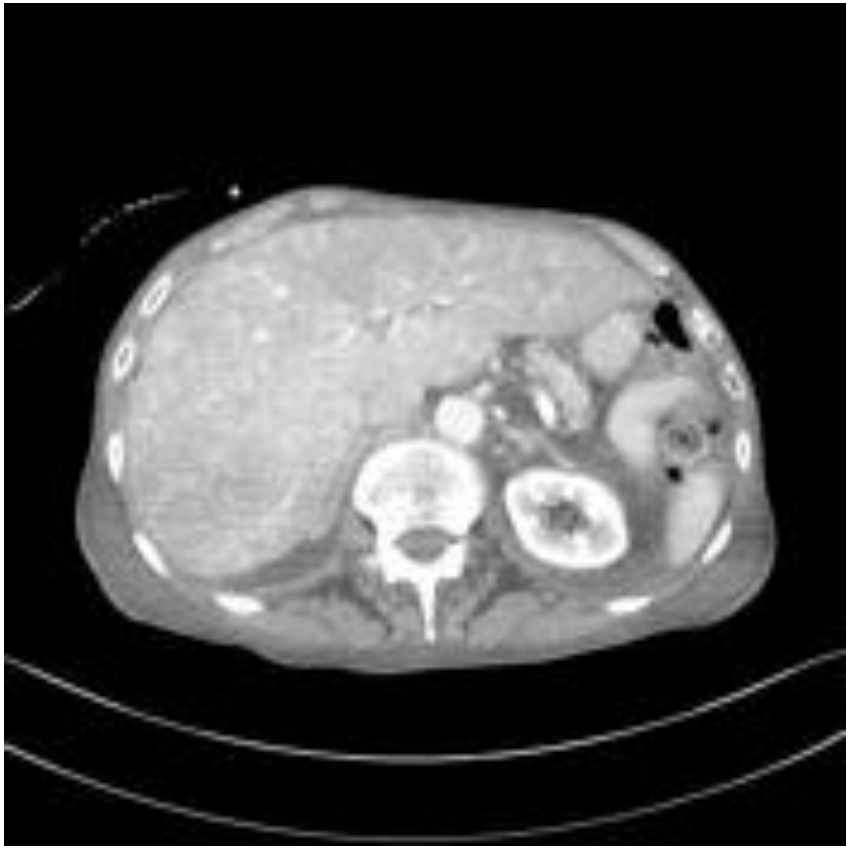
Curve D: Decompensated LV failure despite increase in preload, SV remains low and heart is over stretched



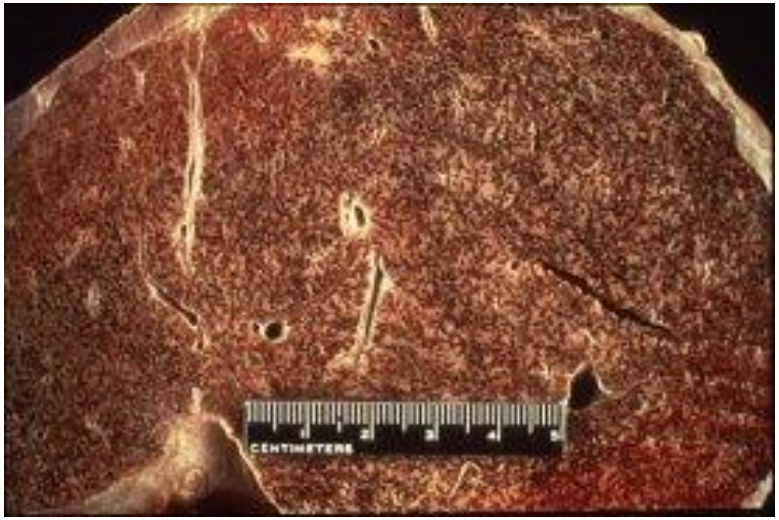
https://s3.amazonaws.com/classconnection/550/flashcards/1323550/png/screen_shot_2015-01-29_at_74853_pm-14B388730333E8C909C.png

“Bat wing” characteristic of pulmonary edema.

Hydrostatic change related to increased LV/LA pressures.

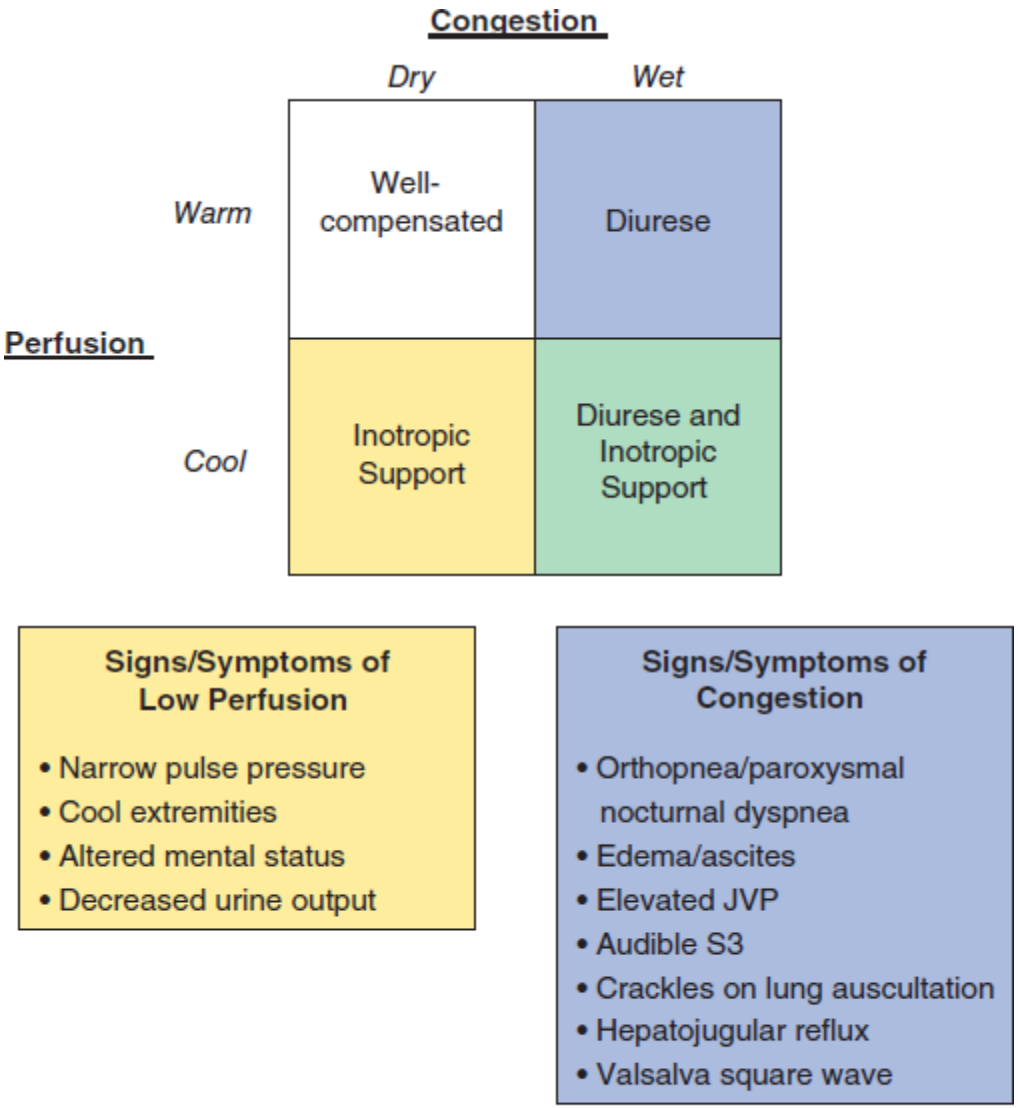


https://images.radiopaedia.org/images/10424854/924d118bde05941134796f25fbdeca_thumb.jpeg

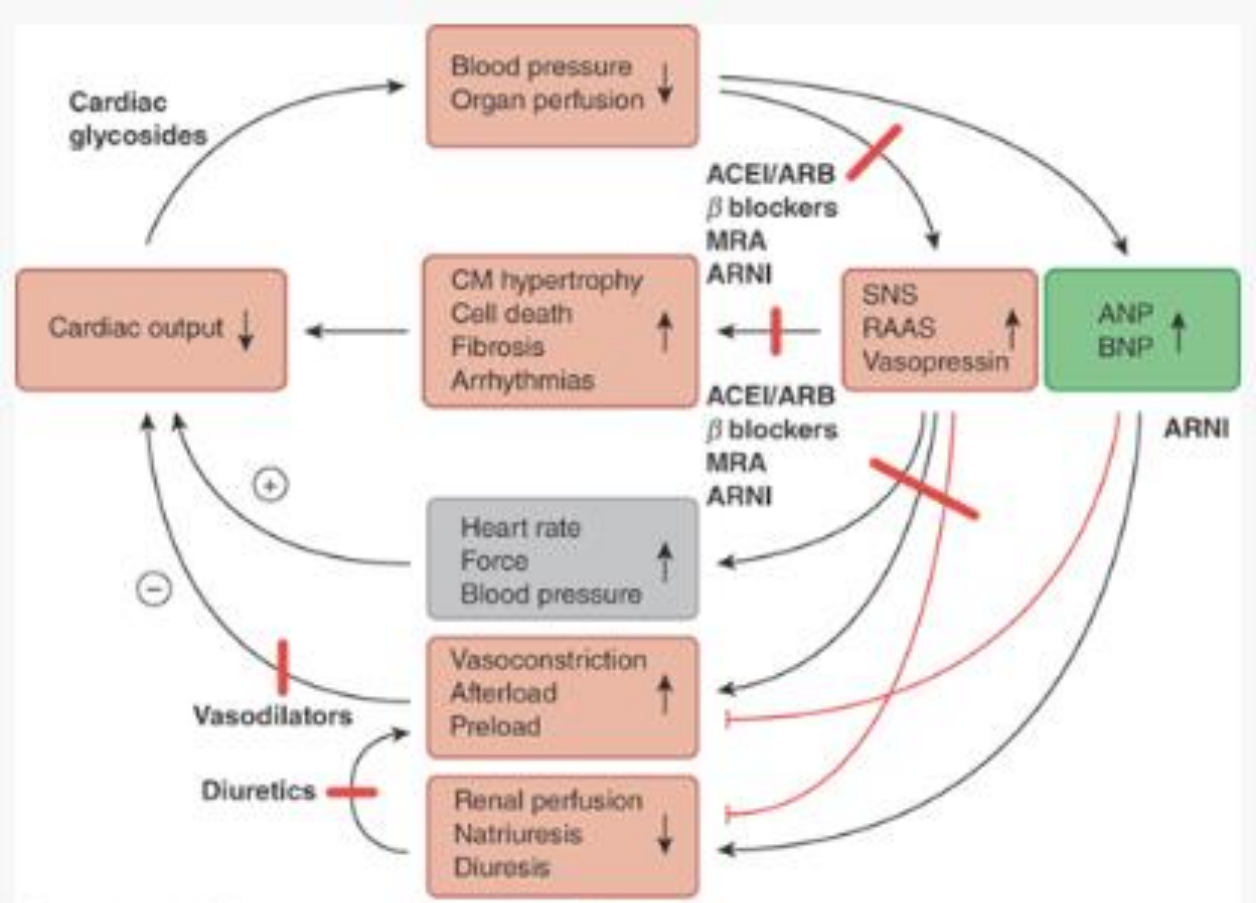


Passive congestion of the liver (“nutmeg liver”) in right heart failure

https://66.media.tumblr.com/tumblr_m081oclMX91rq3lp6o1_400.jpg



Source: Navin Kumar, Anica Law: Teaching Rounds: A Visual Aid to Teaching Internal Medicine Pearls on the Wards
www.accessmedicine.com



Remodeling

- Biological overexpression of compensatory neurohormonal factors lead to left ventricular remodeling
- There is a change in ventricular mass, volume, and shape to cope with the altered hemodynamic demands
- Neurohormonal factors (vasoconstrictors):
- Norepinephrine
- Angiotensin II
- Inflammatory cytokines
- Endothelin
- Reactive oxygen species

Renin-fluid feedback mechanism

- When cardiac output falls, renin release increases and stimulates production of Angiotensin I (AT I).
- Vascular endothelium converts AT1 to AT II
- Systemic vasoconstriction (AT I receptors)
- Arterial pressure increases
- Aldosterone production release increases
- Tubular absorption of Na+ increases at the expense of K+ and H+
- Water retained (also vasopressin mediated)

Renin-fluid feedback mechanism

- Norepinephrine released from sympathetic nerve endings
- Norepinephrine uptake from sympathetic nerve endings is inhibited
- Enhanced α-adrenergic activity
- The renin-fluid feedback control mechanism does not stop functioning until the arterial pressure returns to its original control level
- Natriuretic peptides have a counter-regulatory effect on renin-angiotensin system

Natriuretic Peptides

- Atrial and Brain Natriuretic Peptides respond to volume expansion
- Bind to Na^+/K^+-ATPase.
- Inhibit Na^+ transporter in the nephron
- Increase GFR and filtration fraction
- K^+ sparing
- Decrease renin release
- Alter intracellular Na^+ gradients in vascular smooth muscle cells
- Vasodilatation of veins and arterioles
- Indirectly inhibit the Na^+/Ca^{2+} exchanger causing intracellular calcium to rise in vascular smooth muscle cells

Natriuretic Peptides

- Myosin light chain phosphorylation leads to contraction
- Relaxes as cAMP generated
- ANP and BNP facilitate cGMP formation, leading to myocyte relaxation
- When binding sites are saturated (contractility maximized), Ca^{2+} enters mitochondria, reducing ATP production
- Profibrotic in heart and kidney
- Associated with Calcium accumulation in coronary arteries as well as heart valves
- Implicated in the pathogenesis of hypertension

Table 4 – Comparison between the patients' characteristics in relation to BNP values ≥ 1,400 and <1,400 pg/dL

	BNP		
Characteristics	≥1,400 pg/dL (n = 78)	<1,400 pg/dL (n = 110)	p
Age (years)	58.7 ± 15.0	58.9 ± 14.0	0.901
Male gender - n (%)	44 (56.4)	65 (59.1)	0.714
Cause of HF - n (%):			
Chagasic	29 (37.2)	20 (18.2)	0.003
Ischemic	15 (19.2)	34 (30.9)	0.072
Non-ischemic (non-chagasic)	34 (43.6)	56 (50.9)	0.322
Vasoactive drugs - n (%)	57 (73.1)	57 (51.8)	0.005
LVEF (%)	23.5 ± 6.6	28.3 ± 10.8	0.002
Baseline urea (mg/dL)	92.0 ± 45.4	74.5 ± 40.6	0.002
Baseline creatinine (mg/dL)	1.7 ± 0.7	1.6 ± 0.7	0.102
BNP (pg/dL)	2,734.0 ± 995.4	781.5 ± 341.8	<0.001
In-hospital death	17 (21.8)	12 (10.9)	0.042
1-year death	40 (51.3)	36 (32.7)	0.011

HF: Heart failure; LVEF: left ventricular ejection fraction; BNP: type-B natriuretic peptide.

BNP >600 pg/dL associated with cardiogenic disease
BNP levels also reflect 30 and 180 day mortality post surgery

http://www.scielo.br/img/revistas/abc/v100n3/en_a11tab04.jpg
Accessed 01/10/2020

Energy reserves

- The myocardium contains a low concentration of high-energy phosphates
- ATP levels are buffered in the heart by the much larger concentration of phosphocreatine (PCr), which regenerates ATP, by the creatine kinase (CPK) catalyzed reaction: ADP + PCr = ATP + Cr.
- Regeneration of ATP from PCr can protect the heart from ATP depletion during a mild or brief increase in energy demand, but the heart is fundamentally dependent on continuous resynthesis of mitochondrial ATP.

Energy reserves

- Under normal resting conditions, the heart generates 60% to 70% of its ATP from β oxidation of free fatty acids and 30% from metabolism of carbohydrates.
- During exercise, the large amount of lactate produced by skeletal muscle becomes a major substrate, entering the Krebs cycle after conversion to pyruvate.
- Oxidation of free fatty acids is inhibited, and carbohydrates become the predominant substrate for energy metabolism
- <u>This is also the case in the failing heart.</u>

The failing heart

- With failure, Ca^{2+}-ATPase leads to elevated levels of intracellular Ca^{2}.
- In the mitochondrion, activation of phospholipase and sphingomyelin pathways
- Generation of breakdown products such as free fatty acids and ceramide are seen.
- High conductance ion channels are opened on the inner membrane
- Cytochrome c leaks into cytosol.
- ATP generation falls.
- Apoptosis triggered.

The failing heart

- As ATP needs are greater with enhanced contractility in the compensating heart, the end result is lowering of ATP stores and diminished contractility with development of failure
- ATP depletion by 5-10% (failure of Na^+-K^+-ATPase) leads to entry of Na^+ into cell, K^+ efflux, cell swelling, and dilation of endoplasmic reticulum.

Hemodynamics

- Cardiac output = venous return
- Point of equilibrium is at right atrium
- Poiseuille's Law
- Flow rate = Difference in arterial pressure divided by the systemic resistance and venous pressure divided by venous resistance
- Velocity of flow = Flow/ Cross Sectional Area
- Elastic recoil permits large vessels to expand to handle volume at high pressure and to maintain blood flow at diastole

Arterial structure

- The intima normally consists of a single layer of endothelial cells sitting on a basement membrane underlaid by a thin layer of extracellular matrix
- The intima is demarcated from the media by the internal elastic lamina.
- The media of elastic arteries (e.g., the aorta) has a high elastin content
- Vessels expand during systole and recoil during diastole
- Large vessels
- May become ectatic with aging

Arterial structure

- In muscular arteries, the media is composed predominantly of circumferentially oriented smooth muscle cells
- Regulated by inputs from the autonomic nervous system, and local metabolic factors
- The adventitia lies external to the media and in many arteries is separated from the media by a well-defined external elastic lamina.
- The adventitia consists of loose connective tissue containing nerve fibers and the vasa vasorum (small arterioles that are responsible for supplying the outer portion of the media of large arteries with oxygen and nutrients.

Capillaries, veins, lymphatics

- Capillaries are approximately the diameter of a red cell
- They have an endothelial cell lining but no media
- Variable numbers of pericytes, cells that resemble smooth muscle cells, typically lie just deep to the endothelium.
- Veins have larger diameters, larger lumens, and thinner and less organized walls
- Lymphatics are thin-walled channels lined by specialized endothelium
- Provide conduits to return interstitial tissue fluid and inflammatory cells to the bloodstream.

Hemodynamics

- Arterioles site of greatest resistance
- Circular smooth muscle contains both α_1- and β_2-adrenergic receptors
- Venous system as capacitor (storage)
- Also contains post-ganglionic α_1- adrenergic receptors
- Lowest velocity in capillaries, permitting nutritional flow to tissues

Hemodynamics

- Resistance to flow
- $R = 8\eta L/\pi r^4$ where η is viscosity and L (length) and r (radius) refer to vessel
- Primary determinant of viscosity is hematocrit
- Reynold's number gives probability of turbulence in vessel
- R=2r x Velocity x Density
- R>2000 Turbulent flow, not Laminar flow

Hemodynamics

- In any organ, resistance in series from entering artery to draining vein
- Total resistance is sum of individual resistances
- Flow is same through all resistances, thus pressures adapt
- Liver and intestinal tract connected in series
- Vascular resistance is in parallel
- Total resistance is sum of reciprocal of individual resistance
- Flow is independent of other organ

Hemodynamics

- Laplace's Law
- Wall tension = Pressure/ radius
- Aneurysm
- Dilated ventricle
- Compliance = change in volume/ change in pressure
- Hemorrhage (and venoconstriction) lead to fall in compliance (storage of blood decreases)

Hemodynamics

- Mean arterial pressure = cardiac output x total peripheral resistance
- With standing, pressure and volume in dependent veins increase
- Venous return decrases, stroke volume decreases
- Baroceptor reflex increases sympathetic activity, leading to vasoconstriction and tachycardia with increased venous return and contractility

Pressures in the Pulmonary Circulation	Pressures in the Systemic Circulation
R.Ventricle 25/0 mmHg	L. Ventricle 120/0 mmHg Diastolic = 0-5 or 10
Pul. Artery 25/8 mmHg	Aorta 120/80 mmHg
Mean Pul. Artery 15 mmHg	Mean arterial 93 mmHg Blood pressure
Capillary 7-9 mmHg	Capillary: skeletal – 30 mmHg Renal Glomerular – 50 mmHg
Pul . Venous 5 mmHg	Peripheral Veins 15 mmHg
Left Atrium 5 - 10 mmHg	Right Atrium 0 mmHg 0-2mmHg
Pressure gradient 15 – 5= 10 mmHg	Pressure gradient 93-0= 93 mmHg

Pressure profile along the systemic circulation

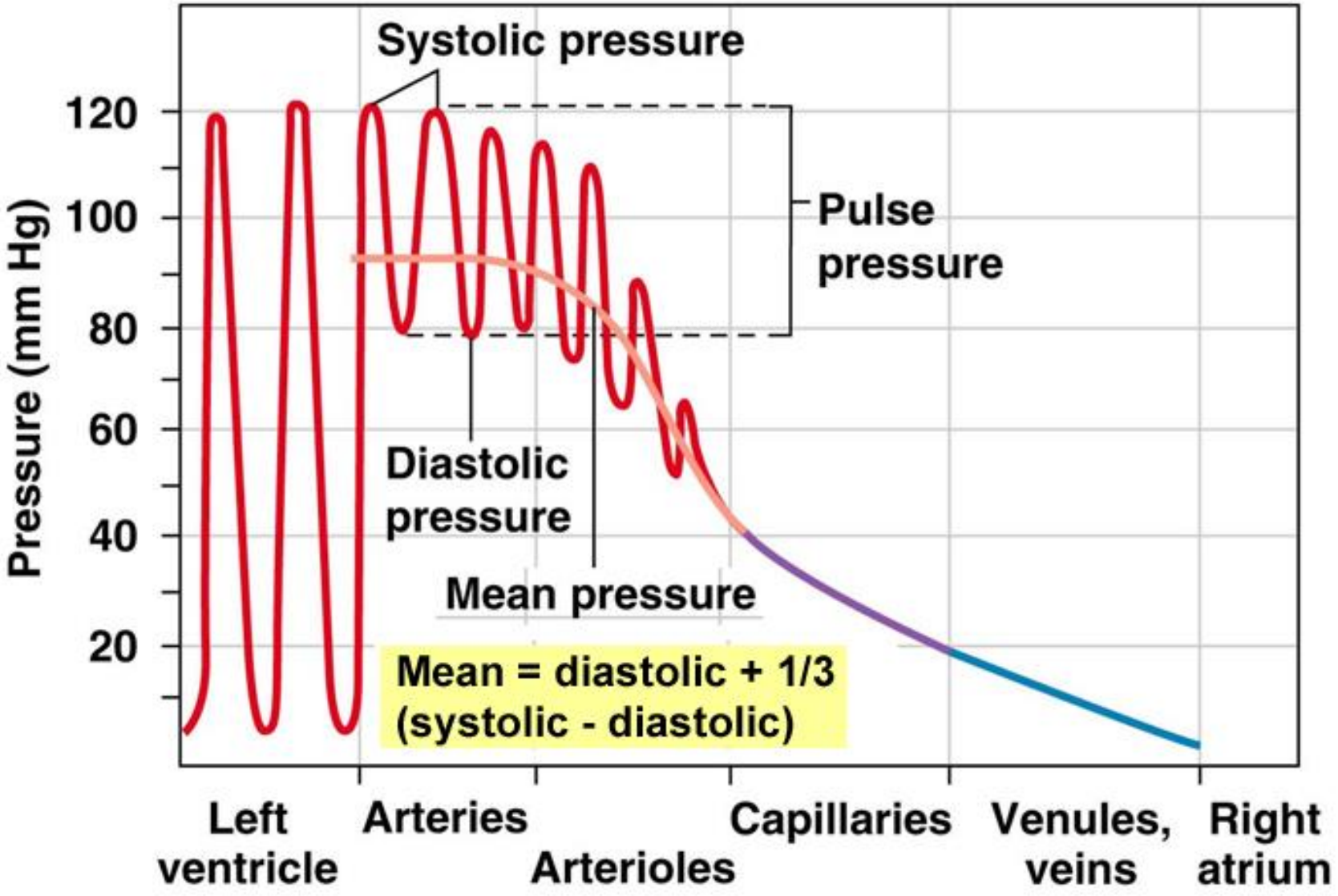


Fig. 15.6

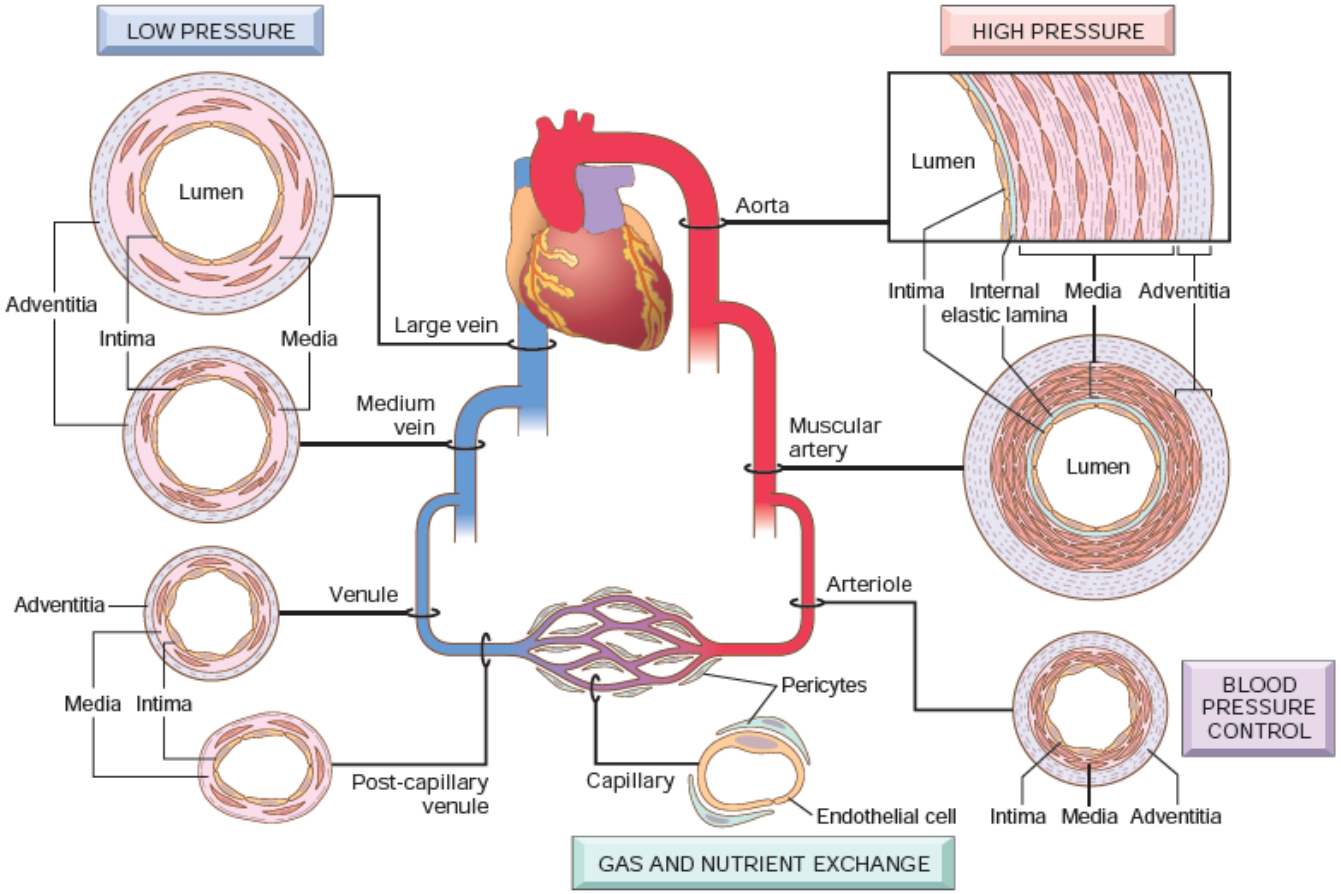


Figure 11-1 Regional specializations of the vasculature. Although the basic organization of the vasculature is constant, the thickness and composition of the various layers differ according to hemodynamic forces and tissue requirements. The aorta has substantial elastic tissue to accommodate high pulsatile forces, with the capacity to recoil and transmit energy into forward blood flow. The muscular arteries and arterioles have concentric rings of medial smooth muscle cells whose contractile state regulates vessel caliber and, thereby, blood flow and blood pressure. The venous system has relatively poorly developed medial layers that permit greater capacitance. The capillary wall permits ready diffusion of oxygen and nutrients because it is comprised only of an endothelial cell and sparse encircling pericytes. The differing structural and functional attributes leave the various parts of the vascular tree vulnerable to particular disorders. Thus, loss of aortic elastic tissue in a large artery may result in aneurysm, while stasis in a dilated venous bed may produce a thrombus.

Compliance

- Systolic pressure directly proportional to stroke volume and inversely proportional to arterial compliance
- Diastolic pressure directly proportional to total peripheral resistance, stroke volume, and arterial compliance

Hemodynamics

- Above the heart level systemic arterial pressure progressively decreases
- Venous pressure at heart level is zero
- Venous pressure above heart becomes sub-atmospheric (negative)
- Surface veins above the heart cannot maintain significant pressure below atmospheric

Hemodynamics

- Deep veins and those inside the cranium can maintain a pressure that is significantly below atmospheric
- Mean pressure in the Saggital sinus is -10 mmHg
- As a consequence of the preceding is that a severed or punctured vein above heart level has the potential for introducing air into the system (Air embolism)