Problem Solving Exercises in Cardiovascular Physiology and Pathophysiology

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Some notes on terminology:

Unless otherwise specified,

- the term BP refers to systemic arterial blood pressure obtained in the brachial artery held at the level of the heart, and mean arterial pressure refers to mean systemic arterial pressure.

- stroke volume, end-diastolic volume, end-diastolic pressure, and ejection fraction, refer to parameters of the left ventricle.

- systolic pressure, diastolic pressure, pulse pressure, mean arterial pressure all refer to pressures in the systemic arteries.

Any other usage of these terms should be with appropriate qualifications; example, pulse pressure in pulmonary artery.
Questions and Answers:

1. Does constriction of arterioles in finger flexors increase mean arterial pressure (MAP)?
It may or it may not. Vasoconstriction in a tissue (i.e., an increase in Local Vascular Resistance, LVR) does not necessarily increase total peripheral resistance (TPR; aka. systemic vascular resistance (SVR). MAP is the product of SVR and cardiac output, and one cannot predict with certainty if a change in LVR in one tissue will TPR and or cardiac output. Vasoconstriction in certain tissues (example, coronary circulation), may elicits a reflex increase in sympathetic discharge. This may result in an increase in TPR. Myocardial ischemia, CNS ischemia, ischemia of metabolically active skeletal muscle, renal ischemia, are all known to elicit reflex increases in sympathetic discharge to resistance vessels that may result in a rise in MAP. Again one cannot predict with certainty; it is best to work backward to reason observations.

2. If the radii of all arterioles in a group of metabolically active forearm flexor muscles doubled, and the mean systemic arterial pressure increased by 50%, to what extent would you expect this to affect blood flow to these muscles assuming no change in viscosity of blood?

The Poiseuille-Hagen equation summarizes the effect of various factors on mean resistance R as follows:

\[ R = \frac{8\eta L}{\pi r^4} \]

Thus, flow \( Q = \frac{\Delta P}{\text{mean } R} = \frac{\Delta P\pi r^4}{8\eta L} \). This equation may be applied to characterize vessels that for practical purposes can be assumed to be rigid tubes with a steady flow rather than pulsatile flow. For the question posed an approximately 24 fold increase in blood flow to the muscles would be predicted. Observed values might depart from this prediction (10-20% either way). In general, as for the magnitude of hyperemia in rhythmically contracting muscle, there is evidence that it can increase as much as 30-fold from baseline. (Ganong, 2005, p. 632).

3. In the upright posture a considerable volume of blood pools in the veins of the lower limb because of the effect of gravity. Does blood normally ‘pool’ (to that extent) in the arteries of the lower limb?
Veins are capacitance vessels and can readily accommodate more blood (of course within limits) relative to the low capacitance, high resistance, high pressure arterial system. Because of the limited compliance (relative to veins), blood does not really pool in the arteries to a significant extent unless there is tremendous arteriolar dilation.

4. In a healthy adult in the upright position, MAP in the brachial artery (at the level of the heart) was found to be 100 mm Hg. In this position, what would the MAP be in a cerebral artery 50 cm above the heart? What would the MAP be in an artery in the foot 100 cm below the heart? How would you expect blood flow to brain tissue 50 cm above the heart and tissue in the feet 100 cm below the heart to compare? Explain.
The magnitude of the effect of gravity on hydrostatic pressure is 0.77 mm Hg/cm at the density of normal blood (there is no need to memorize this). It is important to note however that in an artery in the foot 100 cm below the heart, the mean hydrostatic pressure is 177 mmHg, whereas
in an artery 50 cm above the heart, it is 62 mm Hg [i.e., \(100 - (50 \times 0.77)\)]. However, that gravity has a similar effect on hydrostatic pressure in veins. As a result, the driving pressure is not any different between an artery in the head and an artery in the foot even in the upright posture. Blood flow to a tissue equals driving pressure (perfusion pressure) divided by local vascular resistance. Moreover, flow is regulated by varying local vascular resistance. The point of the question is to exemplify the distinction between driving pressure and hydrostatic pressure. When we talk about BP, we refer to the driving pressure; everywhere in the systemic arteries it is normally the same and it is simply considered to be the MAP at the level of the heart. If the question is whether gravity has an effect on the absolute value of driving pressure (blood pressure), the answer is it may as a result of the reduction in venous return associated with upright posture.

5. During exercise, a healthy 30-year-old male with no evidence of cardiac shunts consumes 2 liters of oxygen per minute. His brachial artery \(\text{O}_2\) content is 200 ml/L and the oxygen concentration of mixed venous blood obtained from the pulmonary artery is 100 ml/L. What is his cardiac output?

Fick’s principle states that the amount of a substance consumed by an organ per unit time (A) = A-V conc. difference of that substance × blood flow through that organ or vascular bed.

Thus, blood flow (Q) = Amt. of the substance consumed / A-V concentration difference for that substance

Fick principle is an application of the law of conservation of mass. For cardiac output estimation, \(\text{O}_2\) uptake by the lungs which equals oxygen utilization by systemic tissues has been used as the indicator substance. \(\text{O}_2\) consumption = 2 L/min = 2000 ml/min. Systemic arterial \(\text{O}_2\) = 200 ml/L. Since there are no shunts, pulmonary artery blood represents fully mixed systemic venous blood, and its oxygen concentration is 100 ml/L. Thus, cardiac output = 2000 / (200-100) = 20 L/min.

6. In a 6-year-old child with tetralogy of Fallot, the hematocrit was observed to be 60. What is its likely impact on ventricular afterload?

An increase in hematocrit from 35 to 50 does not increase viscosity appreciably but increases oxygen carrying capacity of blood considerably. Whereas, an increase in Hct from 40 to 60 doubles viscosity of blood effectively doubling vascular resistance and consequently the load on the heart, and this partly offsets advantages accruing from an increase in oxygen carrying capacity of blood to some extent. (See Boron, p. 457, Fig 18-8).

7. Thin walled capillaries do not burst when they are exposed to a pressure as high as 40 mm Hg. How can this be explained?

For a thin walled structure like a capillary, Laplace’s law is written as \(P = \frac{T}{r}\) where \(P\) is distending pressure, where \(T\) is wall tension and \(r\) is the radius. (Boron pp. 476-477). The distending pressure of blood in the capillary stretches the capillary increasing the passive tension in its wall. Because of its small radius (5 microns), the amount of passive tension needed to
withstand the pressures it is normally exposed to it is small. In contrast, the aorta is exposed to a pressure of about 120 mm Hg with every heartbeat. To withstand this distending pressure, the aortic wall tension is about 1000 times greater, and the aorta is much thicker. In this regard, arterioles have a very important function; if it were not for the relatively high resistance of arterioles, much higher pressures would be transmitted to capillaries.

8. Examine this EKG. Calibration is standard (10 mm = 1 mV, and speed is 25 mm/s). What is the heart rate and rhythm?


RR intervals are fairly regular and the HR averages approximately 75 bpm. Regarding rhythm, analysis of rhythm can be broken into two parts: Is this sinus rhythm? If the rhythm is sinus, the impulse exciting the ventricle originated in the SA node. If it is not sinus rhythm, then what is the rhythm?

The 12 lead EKG along with a rhythm strip should be examined for this:
- P wave is upright in lead II and inverted in aVR, or P should be upright in leads I, II and III.
- Each P wave is followed by a QRS complex
- Every QRS complex is preceded by a P wave
- PR interval is normal.
- QRS duration is normal.
- QRS rate is between 60-100 bpm. (Some build in this criterion and consider sinus tachycardia and sinus bradycardia as arrhythmias. Some consider sinus bradycardia and sinus tachycardia simply as abnormalities of rate rather than rhythm.)
- Additionally, if checked, RR interval length may be seen to vary with the phase of breathing (see below).

The positive terminal of lead II corresponds to + 60 degrees in the hexaxial reference system. The positive terminal of aVR corresponds to minus 150 degrees. If the P wave vector approaches the positive terminal of lead II and moves away from the positive terminal of aVR, it will produce an upright deflection in lead II and a negative deflection in aVR. Sinus rhythm and sinus arrhythmia (described below) allow atrial contractions to contribute to ventricular filling. This coordination is lost with all other arrhythmias including atrial fibrillation, ventricular tachycardia. Thus, for a given HR, sinus rhythm produces the most ventricular filling, all other variables affecting filling remaining the same.

9. In the EKG below, what is the mean electrical axis? What is the likely mechanism of the irregularity of RR intervals in the EKG below? RR intervals happened to be shorter during inspiration and longer during expiration although the phase of breathing is not marked in the EKG below.


The QRS deflection is close to (although not exactly) null or equiphasic in lead I. The lead perpendicular to lead I is aVF. Since the QRS complex is upright in aVF, the QRS axis is + 90 degrees.
In the EKG above, RR intervals are shorter (i.e., instantaneous HR increases) during inspiration and lengthen (i.e., instantaneous HR decreases) during expiration. Furthermore, the rhythm is sinus. Since this phenomenon is linked to breathing and occurs at the same frequency as breathing frequency, it is called respiratory sinus arrhythmia (RSA). It is a physiologic phenomenon. It has traditionally been quantified at the bedside during timed deep breathing at 6 breaths per minute (5 seconds for inspiration and 5 seconds for expiration), and its magnitude is highest at this breathing rate. In healthy individuals, respiratory sinus arrhythmia at rest and during deep breathing is almost abolished by atropine suggesting that the beat to beat variability in RR intervals is mediated primarily by changes in vagal efferent outflow to the heart.

There is evidence that RSA is due to central coupling of respiration and vagal efferent activity to the heart. Fluctuations in venous return, cardiac output and blood pressure may cause baroreflex-mediated oscillations in RR interval at respiratory frequency, and afferent input from stretch receptors in the lungs is also involved. Clinically, a reduction in resting sinus arrhythmia is an early indication of autonomic neuropathy in a variety of conditions including longstanding diabetes. A reduction in RR interval variability during deep breathing has been shown to be a sensitive predictor of mortality in individuals with a myocardial infarction (Katz et al. 1999).

10. Depolarization and repolarization are electrically opposite processes. However, typically, in a given lead, QRS and T waves are both upright (or in the same direction) in a given lead. What does this mean?
This means that repolarization vector is proceeding in a direction opposite to depolarization. Ventricular depolarization progresses from the endocardial aspect of the myocardium to its epicardial aspect. The epicardial aspect of myocardium repolarizes first and the inner layers repolarize later.

11. What is the abnormality noted on the EKG below?

The arrow points to a bizarre QRS complex; in this case, ventricular depolarization begins earlier than the next expected sinus depolarization. The duration of the premature QRS complex is prolonged so it has not conducted through the normal conduction pathway (bundle of His, bundle branches, and Purkinje fibers), which conducts fast (4 m/s). Instead, it has slowly propagated via gap junctions in ventricular myocardium and excited the ventricle. This is a premature ventricular depolarization (PVD). Note the PVD is followed by a ‘compensatory pause’; i.e., the time duration between the R wave just before and the R wave right after the PVD is roughly
equal to the duration of two sinus cycles. The sinus depolarization that arrived at the AV node during the PVD would have been blocked at the refractory AV node. Since conduction through the AV node is unidirectional, a PVD is invariably not conducted to the atria; therefore it does not reset sinus rhythm (compare it with a premature atrial depolarization, see below). A PVD reflects the automaticity of an ‘ectopic’ focus. In terms of action potentials, excitation of a ventricular myocyte during the relative refractory period may result in a PVD. This rhythm strip http://www.youtube.com/watch?v=L19k4CwHMxw also shows PVDs.

A PVD is an EKG finding. This EKG finding per se should not be called premature ventricular contractions since the EKG records electrical not mechanical phenomena. If the PVD does produce a premature ventricular contraction, whether a pulse is felt or not depends on the stroke volume of the extrasystole. The filling may have been poor as to result in a ‘missed beat’ (the heart beats but there is not a pulse). Thus, PVDs are also a cause of ‘pulse deficit’. The beat following a PVD may result in a stronger pulse (postextrasystolic potentiation). This is in part to due to a higher end-diastolic volume for the next beat.

12. Mr. Sanders, a 60-year-old man, presents with a history of palpitations and has evidence of poorly controlled hypertension. Physical examination revealed a HR of 120 bpm (by auscultation). In contrast, pulse rate was 100 bpm and the pulse was irregularly irregular. What does this suggest?

Heart rate is the number of times the heart beats per minute. Pulse rate is the number of times the arterial pulse is felt per minute. Normally, every heartbeat results in a pulse, and invariably one measures HR by counting the arterial pulse. However, some heartbeats may not be strong enough to result in a palpable pulse. This difference (HR minus pulse rate) is called pulse deficit. If one senses beats missing on pulse palpation, it is appropriate to have two individuals simultaneously auscultate the heart and palpate the pulse to quantify pulse deficit. A pulse deficit that is associated with an irregularly irregular pulse is usually due to atrial fibrillation. The unpredictable irregularity of the pulse is because some of the chaotic atrial impulses (we don’t see) are conducted to excite the ventricle whereas some are not. The pulse deficit reflects the fact that not all ventricular beats have a stroke volume good enough to produce a pulse whereas they produce heart sounds.

13. What is the EKG abnormality in the lead II rhythm seen at http://www.youtube.com/watch?v=I1lyBZR82dQ

Premature QRS complexes are frequently seen (the term premature refers to the fact that it occurs earlier than the next expected sinus depolarization). Premature QRS complexes are preceded by a P wave, which sometimes is biphasic (rather than just being upright in lead II). PR interval is normal and the duration of the QRS is normal indicating that it was conducted through the bundle of His, bundle branches and Purkinje system. Therefore, this impulse likely has originated somewhere in the atrium. These premature depolarizations are called premature atrial depolarizations (PADs). They are examples of ectopic beats. PADs are propagated to the sinus node and may therefore ‘reset’ the sinus rhythm without a compensatory pause. PADs result in atrial contraction and therefore produce an ‘a’ wave on the JVP.
14. How you would interpret HR in the EKG below? Calibration is standard (10 mm = 1mV), and it was recorded at a speed of 25 mm/s.

Based on the context, one needs to determine if reference is being made to average heart rate or something else. If HR is determined by auscultating the heart for one full minute, count the number of cycles, it is **average heart rate**. If we count the number of cardiac cycles in 10 seconds and multiply that by six, again, we are estimating average HR. One may also speak of **instantaneous heart rates**, such as by looking at 1 RR interval, and say **at this instant the heart rate is 100 beats per minute**, just like the tachometer in a car shows instantaneous speeds. EKG rhythm monitors show HRs over shorter and shorter periods of time. The EKG above exemplifies the fact that averaging may obscure important information contained in transients; there is no electrical activity in the ventricles for about 5 seconds, and we may say that at the instant marked by brackets the heart stopped. Lack of electrical activity for 2 seconds is defined clinically as electrical asystole. This individual lost consciousness as soon as his heart stopped and regained consciousness 30 seconds later upon achieving recumbency. The bottomline is that if cardiac cycle duration changes abruptly, then HR should be calculated over shorter periods of time to correctly interpret underlying physiology.

15. Mr. Smith, a 60-year-old man, presented with crushing chest pain, diaphoresis, and breathlessness in the past 1 hour. The Standard ECG reveals > 2 mm ST segment elevation in leads I, AVL, V5 and V6. He was diagnosed with acute lateral wall ST segment elevation myocardial infarction. If ST segment elevation occurs in myocardial infarction, what is the underlying mechanism?

The mechanisms are incompletely understood but this is what has been postulated. First, the infarct is deprived of blood supply. With ATP depletion, its RMP becomes less negative. Remember, the Na-K ATPase is an electrogenic mechanism that contributes a bit to making the RMP negative inside (with respect to the exterior). The other reason RMP becomes less negative in the infarct zone is potassium (the most abundant intracellular cation) is lost from injured cells.

Thus, as depicted in the schematic above, extracellularly, the infarct zone, at rest, becomes negative with respect to surrounding normally polarized tissue. Therefore, during diastole, extracellularly, current flows into the infarct. This is what is called the **diastolic current of injury**. TP segment, the EKG segment corresponding to ventricular diastole, is normally isoelectric because normally there is no current flow during diastole. The current flow into the
infarct during diastole depresses the baseline, i.e., the TP segment is depressed. However, the arrangement in ECG recorders is such that TP segment depression is recorded as ST segment elevation.

Secondly, the infarct depolarizes late with respect to surrounding normal tissue probably due to a decrease in velocity of conduction of impulses in the infarcted tissue; the effect of this late depolarization is to simply delay the QRS complex, causing ST segment elevation.

Thirdly, ischemic myocardium repolarizes faster due to accelerated opening of potassium channels. *(One can’t predict this from first principles; it simply, is a property of potassium channels in the myocardium)* Normally, ventricular repolarization is evident as the T wave. But the effect of early repolarization is also ST segment elevation.

Thus, myocardial infarction is characterized by ST segment elevation in leads facing an acute myocardial infarction (Ganong, 2005, pp. 563-4). It should be added that the definition of an acute myocardial infarction has evolved over the years, and now non-ST segment elevation myocardial infarction (NSTEMI) is an entity distinguished from ST-segment elevation MI (STEMI). Thus, based on recent definitions of MI, not all MIs cause ST segment elevation. But when ST segment elevation does occur in multiple contiguous leads, the mechanisms are believed to be those described above.

16. **From a physiologic perspective, which is a better index of ventricular preload – LVEDV or LVEDP?**

Literally, it is the load on a muscle *before* it contracts. The load placed on the ventricle before it contracts is the blood it is filled with. In the ventricle, preload (= end-diastolic fiber length) varies directly with end-diastolic volume. For a working definition, preload is best defined as end-diastolic volume in the respective chamber. (Rothe, 2003; Kass, 1995). In experimental as well as clinical studies, LV end-diastolic pressure (LVEDP), which is estimated by measuring pulmonary capillary wedge pressure, has been equated with preload. The justification for this is that ventricular volumes cannot be reliably estimated by two-dimensional echocardiography, but now LVEDV can be reliably estimated by real time three-dimensional echocardiography.

If left ventricular compliance is normal, LVEDP is proportional to LVEDV. However, clinically, left ventricular compliance is frequently diminished (example, due to concentric hypertrophy, restrictive cardiomyopathy, and hypertrophic cardiomyopathy). In these cases, LVEDP rises out of proportion to LVEDV, and the stroke volume may or may not be directly proportional to the prevailing LVEDP. This is why it is preferable to use LVEDV as the working definition for LV preload. (Kass, 1995)

17. **Mr. John and Mr. Kaufman are both 30 year old healthy men with a resting pulse rate of 75 bpm, regular. Their blood pressures, measured in the sitting position, were respectively 120/60 and 100/70 mm Hg. Would they both have the same cardiac output?**

Both BP values correspond to a MAP of approximately 80 mm Hg. (When HR is between 60 and 100 bpm, MAP is calculated as diastolic pressure + 1/3rd of pulse pressure.) Since both are healthy and normotensive and have the same pulse rate, the one with a higher pulse pressure is more likely to have a higher cardiac output. The point is it is insufficient to interpret MAP as
averaging obscures the scatter around the mean. Diastolic pressure, pulse pressure, and systolic pressure have all got to be carefully looked at. That takes us to the next few questions.

18. Consider the following 2 scenarios: Mr. X, a 45-year-old man, has a resting BP of 120/40 mm Hg. His pulses are bounding, and auscultation reveals an early diastolic murmur in the lower left sternal edge. The PMI is hyperdynamic and seen in the 5th left intercostal space lateral to the mid-clavicular line. What are the physiologic correlates of diastolic arterial pressure?
Flow in the arterial system is pulsatile. That is, flow, resistance and pressure in the arterial system vary continually during a cardiac cycle from a minimum to a maximum.

DP and PP are both instantaneous pressures. Each instantaneous pressure is a product of some volume (rather than flow) of blood in the arterial system and resistance to flow at that point in the cardiac cycle.

DP is defined as the minimum pressure in the arterial system during a cardiac cycle. It is undoubtedly affected by the volume of blood present in the arterial system at that instant, but other than that, physiologically, it reflects the resistance to outflow of blood from systemic arteries. Normally this resistance resides mainly in the systemic arterioles but there are other possibilities as illustrated below.

Some examples of situations changing DP:
• If arteriolar constriction occurs as a systemic phenomenon due to an increase in sympathetic effects on alpha-adrenergic receptors in resistance vessels, the effect of this is to elevate DP.
• Outflow from the arterial system normally occurs via arterioles into capillaries, or via arteriovenous anastomoses into venules, and when one is bleeding (into extravascular space). A 30% decrease in blood volume will very likely drop DP despite adaptive responses.
• Shunting of blood from a large artery into a vein via a large arteriovenous fistula also is characterized by a decrease in DP.
• An abrupt drop in sympathetic discharge to arterioles causes the drop in DP during vasodepressor syncope.

In the problem posed above, the presence of an early diastolic murmur in the lower left sternal edge in association with evidence of an increase in LV radius suggests that aortic regurgitation is the cause of the reduction in the resistance to outflow of blood from the arterial system during diastole. The pulse pressure is elevated most likely because of an increase in stroke volume (see the question below).

19. Consider the following two scenarios. Scenario A - The resting brachial artery BP of Mr. A, 65-yr-old, was 160/80 mmHg. His SV was estimated by Doppler echocardiography to be 80 ml per beat. What is the most likely mechanism of elevation of PP in this individual?

Scenario B - The resting brachial artery BP of Mr. B, 30-yr-old, changes from a resting value of 120/80 mm Hg to 160/80 mm Hg during the 4th minute of treadmill exercise. His
SV at rest was estimated by Doppler echocardiography to average 80 ml per beat. What is the most likely mechanism of the increase in PP in this individual during exercise? During the phase of ejection, a definite volume of blood (approximately 70 ml in a healthy adult at rest) is added to the arterial system. The maximum increment in arterial pressure that occurs with ejection is the PP. The pulse pressure at rest is normally 40-50 mm Hg.

Mr. A has a PP of 80 mm Hg for a SV of 80 ml per beat. In contrast, Mr. B has a PP of 40 mm Hg for the same SV. The other factor that affects PP is compliance of large arteries. With less compliant arteries, a given SV will result in a higher PP. It is important to note that compliance of the arterial system is one of the determinants of ventricular afterload. Stiffer the arteries (i.e., lower the compliance), higher the resistance during ejection of blood. Mr. A appears to have what is called isolated systolic hypertension. His PP at rest is abnormally elevated, however, his DP is WNL. Isolated systolic hypertension is the commonest hemodynamic pattern of primary hypertension in individuals 50 and older (Lilly pp. 307, Fig 13-4), and the underlying pathology is typically atherosclerotic disease of large arteries.

In Mr. B, the increase in PP from 40 to 80 mm Hg during exercise, if assessed, will most likely be accounted for by the increase in SV that occurs during exercise. Large artery stiffness does not suddenly increase significantly during acute exercise. The ratio of stroke volume to PP is an indirect measure of large artery compliance, and this ratio varies directly with arterial compliance.

Thus, large artery compliance is a dynamic resistance factor operative only during the phase of ejection. Because resistance to flow varies from one instant to another during a cardiac cycle, resistance is best described using the term ‘impedance’. Also, several authors continue the use of the term resistance in lieu of impedance.

20. “Afterload is peripheral resistance. Diastolic pressure reflects peripheral resistance. But systolic pressure reflects cardiac output, not peripheral resistance”. Are these statements valid?
The statement that systolic pressure reflects cardiac output and not peripheral resistance is misconceived (see Question 21).

‘Total peripheral resistance’ (TPR, aka. Systemic Vascular Resistance or SVR) has a specific definition. It equals [MAP – MRAP] / cardiac output. Note that TPR actually is an indication of average (rather than total) resistance to flow in the systemic circulation.

However, the word peripheral in the term ‘peripheral resistance’ is rarely explicitly defined. Typically, most sources use the term peripheral resistance to imply the resistance of the small arteries and arterioles to run off of blood in diastole. This implies exclusion of the resistance offered by the arterial system during ejection of blood. When the heart ejects blood into the aorta, the heart is exposed to the physical properties of the aorta and the large arteries (which offer significant resistance to flow; this is called impedance). From a hemodynamic standpoint, even the aorta is ‘peripheral’ to the heart, and there is no reason not to conceive this as a resistance to flow.
In an individual with a BP of 160/80 mm Hg and a stroke volume of 80 ml per beat, is ‘peripheral resistance’ increased? In the view of many, arterial resistance (arterial impedance) is increased. For those that define peripheral resistance as resistance to run off of blood from the arteries, it would be normal.

The term peripheral is easily conceived (as a contrast to the term central) in instances such as peripheral cyanosis, peripheral arterial or vascular disease, and it gets carried over to the term peripheral in ‘peripheral resistance’. That is why the use of the term peripheral resistance without further qualification is confusing. The distinction between varied usages of the term is not trivial when we are trying to understand the hemodynamic correlate of someone with a BP is 170/80 mm Hg. The solution resides in being explicit about what one means by peripheral resistance in hemodynamics, and in separately interpreting diastolic pressure and pulse pressure (see below).

21. B-E below denote resting brachial artery BP values obtained in 4 adult males comparable in terms of age, height, weight, fat mass to A. Interpret the hemodynamic correlates of systolic blood pressure values in each case.

<table>
<thead>
<tr>
<th>Case</th>
<th>Resting BP (mm Hg)</th>
<th>Interpretation, assuming that the BP value was obtained accurately.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>110/70</td>
<td>DP normal; PP normal.</td>
</tr>
<tr>
<td>B</td>
<td>160/120</td>
<td>DP is increased; PP is normal. SP is high simply because DP is high.</td>
</tr>
<tr>
<td>C</td>
<td>160/100</td>
<td>DP and PP are both elevated.</td>
</tr>
<tr>
<td>D</td>
<td>140/50</td>
<td>DP is reduced; PP is increased. Thus, the increase in SP reflects a rise in PP.</td>
</tr>
<tr>
<td>E</td>
<td>90/64</td>
<td>DP is reduced; PP is reduced. Therefore, SP is reduced.</td>
</tr>
</tbody>
</table>

When we measure arterial blood pressure, we measure systolic (SP) and diastolic pressures (DP) and calculate pulse pressure (PP); however, a way to conceive SP is it is the sum of DP and PP. Looks at a BP value and interpret DP and PP separately like I have attempted in the third column above. The physiologic correlates of DP and PP were discussed earlier (see Questions 17-20), and from this follow the interpretation of SP.

The absolute value of DP or PP per se does not, evidently, indicate a specific mechanism for that value. For example, a DP of 50 mm Hg can occur as a result of intense vasodilation during exercise, aortic regurgitation or blood loss. Similarly, a high PP can be due to stiffer arteries or a higher SV or both. The cause should be elucidated considering the context in which the value is observed.

The second thing to note about systolic arterial pressure is this: when aortic valve resistance is normal (i.e., there is no pressure gradient across the aortic valve during ventricular ejection), systolic arterial pressure (measured in the supine position in the brachial artery) reflects LV systolic pressure. This is one reason why systolic arterial pressure per se is an important,
noninvasive physiologic marker of cardiac function. However, when the aortic valve is stenosed, aortic valve resistance becomes a significant determinant of the pressure the left ventricle generates. Depending on the severity of stenosis, the LV generates a much higher pressure, say 160-180 mm Hg instead of the typical 110 mm Hg, to cause the same flow across the aortic valve. Since much of this pressure energy is dissipated in overcoming the heightened resistance imposed by the aortic valve, the SP in the aorta may seem normal, say 110 mm Hg. Thus, in this context, SP in the systemic arteries underestimates LV afterload, since afterload is defined as peak left ventricular wall tension (Lilly, pp. 219, Table 9-1). This is the reason why LV afterload is best defined as ventricular systolic pressure rather than systolic arterial pressure.

To summarize, when trying to interpret the hemodynamic correlates of an elevated or reduced BP, interpret DP and PP separately. A change in DP and or PP will explain the change in SP. Finally, also interpret the absolute of SP; the ventricle generates this pressure, and a higher ventricular systolic pressure correlates with a higher myocardial oxygen demand.

22. **Why is it recommended that BP be measured by the palpatory method before it is determined by auscultation of the brachial artery?**

Systolic pressure should first be estimated by the *palpatory method*, i.e., by inflating the cuff to a value at least 30 mm Hg above the pressure at which the radial or brachial pulse disappears, and determining the pressure at which the pulse reappears. During BP measurement by auscultation, the cuff pressure should be inflated to a value 20-30 mm Hg greater than the systolic pressure value estimated by the palpatory method.

In older patients with a wide pulse pressure, Korotkoff sounds may disappear at values below systolic and then reappear with continued cuff deflation (auscultatory gap) until it finally disappears at the true diastolic pressure. When there is an auscultatory gap and the palpatory method is not used, systolic pressure may be underestimated.

When there is an auscultatory gap and the palpatory method is used, systolic pressure would be estimated correctly (say 210 mm Hg). Korotkoff sounds may cease at some point (say 160 mm Hg). However, if cuff deflation is not continued further at 2 mm Hg since sounds have disappeared, the reading may still miss an auscultatory gap and end up overestimating diastolic pressure as 160 mm Hg. Something like 210/160 mm Hg will be recorded when the actual pressure is 210/100 mm Hg.

23. **The cardiac output of a 50 year old man at rest is 4 L / min; mean HR is 80 bpm. Left ventricular end-diastolic volume (LVEDV) is estimated to average 100 ml. What is the mean ejection fraction?**

Cardiac output = 4 L/min, and HR = 80 bpm. Therefore, mean stroke volume is 4000/80 = 50 ml per beat. LVEDV has been estimated to be 100 ml. Thus, ejection fraction is approximately 50/100 = 0.5 or 50%.
24. You wish to obtain a quantitative estimate of left ventricular filling pressure in an individual with clinical evidence of heart failure (left ventricular S3, low systemic arterial BP, tachycardia, tachypnea and history of effort dyspnea). How would you estimate this? Explain.

Pulmonary capillary wedge pressure (PCWP) reflects left ventricular end diastolic pressure (LVEDP) when there is not any abnormal obstruction to flow from pulmonary capillaries to the left ventricle. If the mitral valve is stenosed, the PCWP may reflect the increased resistance of the mitral valve rather than LVEDP. Another factor to be aware of when measuring PCWP is intrathoracic pressure. For example, if you wish to estimate PCWP in an individual who is being mechanically ventilated with positive end-expiratory pressure (PEEP) included, PEEP will need to be momentarily discontinued when PCWP is estimated. If not, PCWP will reflect intrathoracic pressure instead of ventricular filling pressure.

25. With regard to examining the jugular venous pulse, does it really matter how the patient is positioned?

There are two distinct purposes of examining the jugular venous pulse:

1. Assessing jugular venous pressure (JVP) and using this to estimate central venous pressure (mean RAP). Normally, the upper limit of JVP is 3 cm (some would say 4) above sternal angle at 30-45°, and 8 cm above the midpoint of the right atrium.

2. Examining waveforms of the jugular venous pulse (‘a’ and ‘v’ crests and the ‘x’ and the ‘y’ descents), and using these phasic variations in RAP to make inferences regarding function of the right heart.

This mini-lecture on basic considerations in examination of the JVP may be helpful. http://www.youtube.com/watch?v=uelWjO2U1Hk

The midpoint of the right atrium is commonly accepted as a reference point for pressure measurement in the veins. On the body surface, the manubriosternal angle is assumed to be a vertical distance of about 5 cm from the mid-point of the right atrium whether the individual is supine or standing or reclined at an angle. Thus, the patient may be in any position (supine, standing or reclined at 30 or 45°) when the manubriosternal angle is used as the external reference point for assessing JVP.

What is the jugular vein pulse due to?
Flow in veins is nonpulsatil except in those close to the heart. Pulsation in the jugular vein is due to pressure waves transmitted back up from the ‘wall’ of the right ventricle and atrium via the intervening large veins. Net flow in the jugular vein on the other hand, is evidently directed toward the right atrium. Some might think that the jugular vein pulsation normally results from retrograde flow of blood from right atrium into the veins upstream but regurgitation of blood into jugular veins per se is insignificant in the absence of tricuspid stenosis, tricuspid regurgitation or A-V dissociation.

What does one observe in order to estimate jugular venous pressure?
One observes the top of the jugular vein pulsation i.e., the point at which jugular vein collapses.
**Why avoid examining the jugular vein with the individual standing?**
Compared to the supine position or with the body reclined at 45° to the horizontal, venous return is reduced in the upright posture. The magnitude of mean RAP is normally such that the top of the jugular vein pulsation is below the clavicle when the individual assumes the upright posture and one can’t see the pulsations.

**Why avoid examining the jugular vein with the individual supine?**
Compared to the upright posture, venous return is greater in the supine position. So flow in the jugular veins in the supine position may be such that the veins are distended by the higher venous return, and this may obliterate the pulsations transmitted from the right atrium.

**Why is jugular vein pulsation measured with the individual reclining at 45°?**
The magnitude of the mean RAP is normally such that the top of the jugular vein pulsation is at a vertical height of 1-3 cm above the manubriosternal angle, and if it is raised beyond 3 cm, it indicates that right atrial pressure is elevated. When the top of the pulsation is visible, one may then assess the waveforms. Some clinicians start off with the subject’s upper body reclining at 30° to the horizontal and change to 45° if needed.

In some patients, if the JVP is examined with an individual reclined at 45° with the neck muscles appropriately relaxed, the jugular veins may be clearly distended yet the top of the jugular vein pulsation cannot be identified. Other clinical findings may suggest the possibility of congestive heart failure. Try with the subject standing. Standing would reduce venous return to the right side of the heart, and right atrial pressure (and consequently the top of the jugular vein pulsation) may drop to an extent as a result of this. It may be that this individual has a condition such as severe tricuspid regurgitation, constrictive pericarditis or another cause for severe right heart failure. If the top of the jugular vein pulsation becomes visible in the neck with the subject standing, it may be that it was originally so raised as to be within the skull.

This clip (40 sec) [http://www.youtube.com/watch?v=VdgA3fcp7Cs](http://www.youtube.com/watch?v=VdgA3fcp7Cs) shows jugular veins that are so distended but the top of the pulsation is not easy to identify even with the individual standing. This is described to occur in severe tricuspid regurgitation.

**26. Discuss the relationship between changes in heart rate and changes in cardiac output.**
Consider this exchange between a tutor and his student:

**Tutor:** What is the relationship between changes in HR and changes in CO?

**Student A:** cardiac output = HR × SV; thus when HR increases, CO should increase.

**Tutor:** Your answer may be correct in certain situations such as with an increase in HR from 60 to 150 bpm in sinus rhythm in a young healthy adult performing intense exercise. But are there alternate possibilities?

**Student A:** Nothing that I can think of.

**Tutor:** What if an increase in HR is accompanied by a decrease in SV due to some reason such as continuing blood loss? So, in responding to my question, you made the assumption that SV would either increase or not change, right?

**Student A:** Yes, it is true, it is important to know what concurrently happens to SV.
Here is another exchange on the same topic with another student:

**Tutor:** What is the relationship between changes in HR and changes in CO?

**Student B:** CO = HR \times SV; when HR increases, time available for ventricular filling decreases; therefore SV decreases (from its baseline value).

**Tutor:** Your prediction may be correct in certain situations, but are there alternate possibilities?

**Student B:** Nothing that I can think of. The text said: as HR increases, the duration of diastole decreases; it also said: tachycardia reduces time available for ventricular filling.

**Tutor:** Those assertions from the text are, by definition, correct. But does a reduction in time available for ventricular filling necessarily result in diminished ventricular filling?

**Student B:** I would think so.

**Tutor:** What happens to CO when a healthy human exercises?

**Student B:** CO should decrease or not change much (from its baseline value).

**Tutor:** OK. Can you think of a situation in which the heart beats faster as well as stronger?

**Student B:** Yes, that happens when we exercise and this allows the heart to pump more blood to tissues; in fact, I’ve observed my pulse rate increasing to 140 per minute and sometimes even more and have felt the heart pounding when working out.

**Tutor:** Good. Do you know the maximum heart rate one can achieve during intense exercise?

**Student B:** I believe maximal heart rate is 220 – (age \times 0.6) bpm.

**Tutor:** Excellent. In a healthy young adult, CO has been observed to normally increase as much as 2-6 fold from its resting value, depending on the intensity of exercise and an individual’s fitness level. If, as you seem to have conceptualized, an increase in HR could only be accompanied by a decrease in SV, how could CO increase as much as six times from baseline during exercise? Does HR alone normally increase 6 times with little change in SV to result in that much increase in CO from baseline?

**Student B:** I get it. So there must be a range of HR values in which an increase in HR may not at least normally be accompanied by a decrease in ventricular filling.

**Tutor:** Though there is more to it, this is a much improved position in that you are now open to considering two diametrically opposite possibilities in a given situation. I encourage you to think of other examples of interactions between variables.

27. In a healthy adult weighing 70 kg and running a treadmill at 10 miles per hour, cardiac output was measured to be twice the baseline, resting value of 5 liters per minute. What would the change in mean arterial pressure be from baseline?

**Student C:** Increase, since mean arterial pressure = CO \times TPR; no, no, I take that back. It would depend on what also happens to TPR.

**Tutor:** Very good. One would need to actually measure MAP and since CO is known, TPR can be calculated. It depends on the intensity of the exercise, and the individual’s response and observation is important.

28. Typically, what happens to the intensity of the murmur of aortic stenosis during a Valsalva maneuver?

Most cardiac murmurs including that of aortic stenosis reduce in intensity during the strain phase (Phase II) of the Valsalva maneuver because of a reduction in venous return to the right ventricle.
and eventually left ventricle. However, the murmur of hypertrophic obstructive cardiomyopathy may become louder since a reduction in venous return further reduces LV volume and worsens obstruction due to asymmetric septal hypertrophy. (Constant, 1999, pp. 225).

29. **Describe how heart failure from volume overload can be distinguished from heart failure due to an intrinsic defect in myocardial systolic and or diastolic function.**

   In terms of ventricular preload, afterload and myocardial contractility, what are the determinants of steady-state mean left atrial pressure (MLAP)?

   A pathological increase in MLAP can occur as a result of 4 distinct causes:

   1. **Excessive ventricular preload (volume overload).** An increase in ventricular volumes in the absence of a primary decline in ventricular systolic and diastolic function.
   2. **Excessive ventricular afterload.** An increase in systemic vascular resistance in the absence of a primary decline in ventricular systolic and diastolic function. Example: uncontrolled systemic HTN.
   3. **Reduction in myocardial contractility** is the only cause of low EF and low cardiac output. The increase in ventricular volume is secondary to poor contractility. Example: a massive acute MI.
   4. **Low preload due to a primary defect in ventricular diastolic function:** Preload (LVEDV) is low because of ventricular diastolic dysfunction (as in concentric LV hypertrophy, restrictive cardiomyopathy) or it may be due to restriction of filling from without (due to constrictive pericarditis, tamponade). SV is low because LVEDV is low. EF is usually normal unless systolic function coexists.

   2 and 3 may coexist, and excessive preloading may occur as a consequence of this.

   If right and left atrial pressures and cardiac output are normalized simply by correcting an increase in blood volume (usually achieved with diuretics or dialysis), then the primary problem is volume overload (**excessive preloading**). This may occur for example in the context of acute renal failure or acute exacerbation of chronic renal failure. The patient may develop symptoms of acute decompensated heart failure and even pulmonary edema (often called **flash pulmonary edema**). When volume overload is corrected, symptoms of heart failure disappear, and ejection fraction and cardiac output may be normalized. Appropriate management of heart failure is aided by identifying the underlying etiology and the underlying hemodynamic mechanism (one or more of the categories above).

30. “Cardiac output steadily rises as RAP falls.” (Boron, p. 571, left column). **Does this relationship hold at all times?**

   What if blood volume reduces due to substantial hemorrhage? Venous return and RAP will fall, but cardiac output falls as well.

31. Figure 23-10 in Boron (p. 571) shows that with increased blood volume, venous return increases. **Does this relationship hold at all times?**
An increase in blood volume (in veins) does not necessarily increase venous return because there are other factors that affect venous return. Individuals with an increased blood volume do not necessarily have an increase in cardiac output. Other factors include tone of venules, capacitance of systemic veins, and the effect of tissue pressure (example, the massaging effect of skeletal muscle contractions).

32. See Figure 23-10B in Boron (p. 571) showing that arterial vasodilation increases venous return without a change in right atrial pressure. But can arterial vasodilation have any other effect on venous return?
Consider a patient who experiences an emotional faint. In the classical form of vasovagal syncope, there is arteriolar dilation (vasodilation) due to abrupt withdrawal of sympathetic discharge to the resistance vessels. Thus, SVR drops greatly. Diastolic pressure may be so low as to be unrecordable. This in turn causes blood to pool in the veins and venous return falls. Venous return is restored after recumbency is achieved.

33. Are diagrams depicting intersection of cardiac function and venous return curves helpful?
Figures 23-11 (A, B and C) in Boron (p. 573) seek to explain how cardiac output and venous return are matched and the relationship of these two variables to RAP. The question of how they are matched does not arise, since in the steady state, in postnatal life, when there are no shunts between the systemic and pulmonary circulations: Systemic Venous Return = Right Ventricular Cardiac Output = Pulmonary Blood Flow = Pulmonary Venous Return = Left Ventricular Cardiac Output = Systemic Blood Flow = Systemic Venous Return

Differences between systemic venous return and cardiac output can only be transient. For example, during deep inspiration, venous return to the right side of the heart may be better in relation to the venous return to the left ventricle but over a period of time the inflows and outputs from the two ventricles must be the same.

Plotting the intersections of the two curves does not add insights beyond what can be gleaned from plotting the relationship between LVEDV and stroke volume or cardiac output (Frank-Starling curve). For example, if the idea were to see if an increase in blood volume in veins increased venous return, one does not need the venous return curve. If an increase in blood volume increased cardiac output without a change in contractility (as noted from the Frank-Starling curve), then it must have been secondary to an increase in venous return. If interested, see http://jap.physiology.org/content/101/5/1523/reply

For Question 28, we derived distinct causes of an increase in LAP (or RAP) from the anatomy of the normal postnatal circulation and principle of conservation of mass but did not use either the vascular function curve.

34. Define heart failure. How is heart failure classified? Define each of the following: systolic dysfunction; diastolic dysfunction; heart failure with preserved ejection fraction;
heart failure with reduced ejection fraction. What is the difference between low cardiac output and high cardiac output heart failure? Define acutely decompensated heart failure and chronic stable heart failure.

There are numerous definitions but none is crisp and specific for heart failure and a precise working definition is difficult. The ACC/AHA consensus definition for heart failure (2013) is: “HF is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary and/or splanchnic congestion and/or peripheral edema. Some patients have exercise intolerance but little evidence of fluid retention, whereas others complain primarily of edema, dyspnea, or fatigue. Because some patients present without signs or symptoms of volume overload, the term “heart failure” is preferred over “congestive heart failure.” There is no single diagnostic test for HF because it is largely a clinical diagnosis based on a careful history and physical examination.” Other conditions (such as chronic obstructive pulmonary disease) that can result in such symptomatology should be excluded.

Heart failure, from a physiologic perspective, can be defined as a condition characterized by diminished cardiac output due to a disease process primarily in the heart, with the result that systemic oxygen delivery is insufficient to meet the demands of tissue metabolism. The sensitivity of this definition is improved by including states in which the maintenance of normal cardiac output can occur only at the expense of elevated ventricular diastolic filling pressures, or by defining heart failure as a reduction in cardiac reserve due to a disease of the heart. Cardiac reserve is the extent to which resting cardiac output can be augmented under conditions of increased demand; it is equal to the difference between maximal cardiac output and resting cardiac output. While resting cardiac output may be preserved in early stages of heart failure, maximal cardiac output is reduced.

A reduction in cardiac output due to a reduction in total blood volume, hypotension due to a primary decrease in systemic vascular resistance, and hypotension due to a tension pneumothorax are all entities distinct from heart failure. Heart failure is one subtype of circulatory insufficiency, and cardiogenic shock is a severe form of heart failure.

Systolic dysfunction: It is a reduction in SV due to a reduction in myocardial contractility or an increase in afterload. Contractility is often mistakenly equated with force of contraction. It is one of three independent determinants of stroke volume, the other two being preload and afterload. Clinically, systolic dysfunction is defined as reduced LV ejection fraction with or without symptoms of heart failure. SV is lower than normal, and resting cardiac output may be maintained by a compensatory increase in HR. Maximal cardiac output (or cardiac reserve) is reduced. As the disease progresses, resting cardiac output reduces as well.

Diastolic dysfunction: It is a reduction in SV due to abnormal diastolic function (due to some cause). The following three criteria need to be fulfilled for this diagnosis (Paulus et al. 2007):

- Low LVEDV or a high LVEDP/LVEDV ratio
- LVEDP > 12 mm Hg or pulmonary capillary wedge pressure > 16 mm Hg
- Normal systolic function (LVEF > 50%)
Dyspnea due to pulmonary congestion is often the earliest symptom of diastolic dysfunction. Several noninvasive indices of ventricular diastolic function that can be obtained by Doppler studies of flow across the mitral valve have also been developed. A prolongation of isovolumic relaxation time also is another index of diastolic dysfunction. In diastolic dysfunction, resting cardiac output may be maintained by a compensatory increase in HR. Maximal cardiac output (or cardiac reserve) is reduced. As the disease progresses, resting cardiac output may decrease as well.

Finally systolic and diastolic dysfunction may coexist.

**Low-output vs. high-output heart failure:** As the term suggests, low-output heart failure is characterized by a low cardiac output. Whether resting cardiac output is low depends on the severity of heart failure. Not all patients with symptoms and signs of heart failure have a lower than normal cardiac index at rest. This is because a reduction in stroke volume is partially compensated by an increase in heart rate. Their exercise capacity is clearly diminished indicating a reduction in maximal cardiac output. When heart failure advances, resting cardiac output declines to low values.

The presence of symptoms and signs of heart failure in the setting of high cardiac output has been termed **high-output heart failure.** It has been described in chronic anemia, hyperthyroidism, A-V fistula and septicemia. The primary hemodynamic abnormality is a reduction in systemic vascular resistance (afterload). The resulting fall in arterial blood pressure is compensated by a reflex increase in cardiac output. Pulse pressure is usually widened (reflecting high stroke volume) and heart rate may be elevated. Despite raised cardiac output, dyspnea may occur. Importantly, although called heart failure, the primary problem is not in the heart. Rather the use of the term emphasizes the notion that the function of the heart is to generate a cardiac output sufficient to meet the demands of metabolically active tissues. The mechanism of dyspnea may differ depending on the underlying etiology. Evidently, vasodilators are not appropriate for managing high output heart failure. Inotropes are not appropriate since systolic function is normal. The underlying etiology should be identified and addressed (Mehta and Dubrey, 2009).

**Acute decompensated heart failure (ADHF):** In ADHF, the development of the heart failure syndrome is dramatic and the patient is acutely breathless at rest (for example, due to acute pulmonary edema secondary to acute mitral regurgitation). ADHF may also represent exacerbation of otherwise chronic compensated (stable) heart failure (see below). The qualifier *decompensated* is used in this context when there is evidence of one or more of the following: **Congestion:** pulmonary venous congestion or frank pulmonary edema; worsening systemic venous congestion; **Low cardiac output:** hypotension; low pulse pressure; signs of systemic hypoperfusion (cold extremities).

Management typically requires hospitalization and prompt intervention. (Lilly, pp. 241; ACCF/AHA, 2013)

**Chronic stable (or compensated) heart failure** is heart failure characterized by absence of decompensation (defined above) and is described in Lilly, pp. 233, Table 9-6.
35. A 60-year-old man with aortic stenosis but normal coronary arteries (on coronary angiography) presents with chest pain particularly during exertion. His HR is 90 bpm, and his BP is 100/70 mm Hg. He has the clinical findings that support the diagnosis of calcific aortic valve stenosis. EKG reveals evidence of left ventricular hypertrophy, ST segment depression and T wave abnormalities in anterior and lateral leads. What are the likely mechanisms of chest pain in this individual?

Whilst the increase in the ratio of wall thickness to cavity radius (called relative wall thickness, h/r) minimizes the wall stress $\sigma$ required to generate sufficient intraventricular pressures in AS, the increase in muscle mass increases myocardial oxygen requirement. Myocardial oxygen demand is directly related to intramyocardial tension and heart rate. A surrogate of myocardial oxygen demand therefore is the product of ventricular systolic pressure and heart rate. Left ventricular diastolic pressure may also be increased if the concentric hypertrophy of aortic stenosis leads to increased ventricular stiffness. As perfusion of left ventricular subendocardial regions occurs mainly in diastole, the decrease in effective perfusion pressure during diastole (i.e., the difference between the mean aortic pressure and intraventricular pressure during diastole) increases the likelihood of myocardial ischemia.

Diminution in ventricular radius minimizes absolute end-diastolic volume; therefore, during exercise, cardiac output can be increased solely by reducing end-systolic volume and by increasing HR. Decreases in coronary blood flow in AS has been explained on the basis of the Bernoulli’s principle. (Ganong, 2005).

**Bernoulli’s principle**

The lateral (distending) pressure drops at the level of the constriction in the figure above. This could be a carotid atheroma, or a stenotic aortic valve. The Velocity of flow increases at the level of the constriction. Also there is a pressure drop from A to B.

Bernoulli’s principle states that the lateral pressure drops at the level of the constriction (marked) in the tube above, and velocity of flow increases at the level of the constriction.

There is a pressure drop distal to the stenotic aortic valve because some of the pressure energy is used to overcome the resistance imposed by the stenotic aortic valve. The magnitude of the pressure drop (LV systolic pressure – systolic arterial pressure) across the stenotic aortic valve is one of the indices of severity of aortic stenosis although it may or may not correlate with symptomatology. The coronary arteries originate just above and at right angle to the stenotic aortic valve. The lateral pressure is reduced at the level of the stenosis (constriction) and there is a pressure drop beyond it. Thus, the driving pressure for coronary blood flow is reduced.
Other mechanisms also contribute to ischemia in aortic stenosis (in the absence of stenosis of epicardial coronary arteries). It includes an increase in coronary vascular resistance due to ventricular hypertrophy and a relative decrease in myocardial capillary density. Finally, the oxygen consumption of the hypertrophied heart is much greater with ischemia ‘relative’ to increased demand. With an increase in heart rate and contractility during exercise, myocardial oxygen demand increases considerably and may not be met by a commensurate increase in coronary blood flow.

36. Which is the emerging method for estimating the hemodynamic significance of a coronary artery stenosis?
From Bernoulli’s principle, it follows that there is a pressure drop distal to an arterial stenosis that varies directly with the resistance offered by the stenosis (say from 100 mm Hg to 60 mm Hg, for an illustration see Fig 17-10 in Boron, p. 440). The pressure distal to a stenosis can be measured with a pressure wire in the coronary artery thin enough that it can be threaded past the stenosis. The hemodynamic impact of this stenosis is better assessed under maximal flow conditions. To achieve these conditions, isosorbide dinitrate (a dilator of epicardial coronary arteries) and adenosine (a dilator of coronary arterioles) are administered into the coronary artery. If the pressure in the coronary artery distal to the stenosis is 60 mm Hg and the pressure just proximal to the stenosis is 100 mm Hg, the fractional flow reserve (FFR) is 0.6 or 60%. The maximum normal value possible is 1. FFR is the ratio of the maximal blood flow through a stenotic artery to the maximal blood flow through the same artery (if it were normal). An FFR less than 75% is invariably associated with signs of myocardial ischemia, and an FFR greater than 80% is invariably not associated with exercise induced myocardial ischemia. FFR measurements are evolving into a gold standard for evaluation of the functional significance of coronary artery stenoses over exercise electrocardiography and other imaging techniques. (Pijls and Sels, 2013).

37. The BP response after 2 min of quiet standing of a 65-year-old man with recent onset lightheadedness was a drop in systolic and diastolic pressures by 20 and 10 mm Hg. Does he have orthostatic hypotension?
Orthostatic hypotension (OH) has been defined as a sustained reduction of SP of at least 20 mm Hg and DP of 10 mm Hg within 3 min of quiet standing. (Within a few seconds of standing, if BP is recorded with a beat-to-beat monitor, arterial pressure may fall to this extent even in apparently healthy individuals but it does not last more than a few seconds, and lightheadedness if any is transient.) It is in reference to this that the word ‘sustained’ is used in the definition of OH. In individuals with supine hypertension, a reduction in SP of 30 mm Hg or more is recommended as the definition. (Freeman et al, 2011). The term orthostatic intolerance (OI) - inability to tolerate standing that is relieved by lying down; it should be limited to referring to a patient’s symptoms (lightheadedness; weakness; fatigue; nausea; blurring of vision). All individuals with OI do not have OH and OH does not necessarily result in OI.
38. An otherwise healthy adult with a BP of 120/80 mm Hg and a HR of 70 bpm suddenly complained of intense presyncope and his BP dropped within 10 seconds to 60/30 mm Hg while his HR was 63 bpm. There was no history of trauma or evidence of blood loss. What is the immediate (meaning, within the next 10 seconds) effect of this fall in BP on systemic venous return? How is syncope classified from a hemodynamic perspective? Give examples of causes.

His diastolic pressure drops by 50% whereas there was only a 10% reduction in HR. Thus the dominant mechanism of hypotension in this case is abrupt arteriolar vasodilation. Now that blood has a greater volume of distribution with a lower driving pressure, venous return (the rate at which blood returns to the right ventricle) would reduce. This will further reduce BP by reducing cardiac output, and very likely precipitate frank syncope. The purpose of this question is to prompt consideration of interaction between variables from observations. If SVR falls by 50%, MAP does not fall by 50%, rather it falls to a greater extent because such a fall in TPR also reduces venous return and thereby cardiac output.

**Syncope** is defined as a transient loss of consciousness and loss of postural tone due to cerebral hypoperfusion, followed by spontaneous recovery without residual neurologic deficit. OH is one cause of syncope. **Presyncope** is usually applied to refer to rapid and often unanticipated onset of lightheadedness, an impending sense of passing out and it may be associated with fatigue, nausea, blurring of vision. *(Compare with orthostatic intolerance)*

Since MAP is the product of cardiac output and SVR, OH is due to either an excessive fall in cardiac output or a defective rise in SVR immediately upon standing. Cerebral blood flow (CBF) = MAP / CVR  
CBF = [CO × SV × SVR] / CVR  
CBF = [HR × SV × SVR] / CVR, where MAP: mean arterial pressure; CVR: cerebral vascular resistance; CO: cardiac output; SV: stroke volume; SVR: systemic vascular resistance (aka. TPR)

Since the initial fall in MAP is because of a drop in venous return and therefore SV, OH occurs as a result of a relatively inadequate rise in HR and or SVR. *(Boron)* Steady state CBF is excellently autoregulated as long as MAP at the level of the heart is between 65-140 mm Hg (in dogs), the ‘limits of autoregulation’. For ethical reasons, the lower limit of autoregulation is not easily investigated in humans, but studies suggest that the lower limit of autoregulation in adult humans may correspond to an MAP in the range of 50-65 mm Hg.

When hypotension is identified as the cause of cerebral hypoperfusion, it is important to identify which component(s) of MAP is/are so low, and what the etiology of hypotension is, as this has implications for treatment. Finally, cerebral hypoperfusion can occur when there is an increase in cerebral vascular resistance even if MAP is normal. This entity has come to be called cerebral syncope. Thus, based on hemodynamic mechanisms, one can classify causes of syncope as follows:

<table>
<thead>
<tr>
<th>Hemodynamic abnormality</th>
<th>Class (examples)</th>
</tr>
</thead>
<tbody>
<tr>
<td>➔ MAP due to a ➔ CO due to disease of the heart</td>
<td>Cardiogenic syncope</td>
</tr>
<tr>
<td></td>
<td>• Aortic stenosis</td>
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</table>
### Hemodynamic abnormality

<table>
<thead>
<tr>
<th>Class (examples)</th>
</tr>
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<tbody>
<tr>
<td>• Hypertrophic cardiomyopathy</td>
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<tr>
<td>• High grade AV block</td>
</tr>
<tr>
<td>• Long QT syndrome</td>
</tr>
<tr>
<td>• Catecholaminergic polymorphic VT</td>
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<table>
<thead>
<tr>
<th>MAP due to defective vasoconstriction and or a decrease in cardiac output within 3 min of standing</th>
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</thead>
<tbody>
<tr>
<td>Syncope due to ‘classic’ orthostatic hypotension (OH)</td>
</tr>
<tr>
<td>• Hypovolemia due to any cause (blood loss; dehydration)</td>
</tr>
<tr>
<td>• As a side effect of therapy with vasodilators particularly in the elderly with hypertension.</td>
</tr>
<tr>
<td>• Idiopathic degenerative disease of sympathetic noradrenergic postganglionic neurons resulting in deficiency of norepinephrine</td>
</tr>
<tr>
<td>• Damage to the afferent limb of the arterial baroreflex arc (such as following neck trauma, irradiation to the neck damaging afferents from arterial baroreceptors)</td>
</tr>
<tr>
<td>• Inherited developmental defects in baroreceptor afferent neurons (familial dysautonomia; Riley-Day syndrome)</td>
</tr>
<tr>
<td>• Loss of function in alpha-adrenergic receptors</td>
</tr>
<tr>
<td>• Dopamine beta-hydroxylase deficiency (and therefore deficiency of norepinephrine and epinephrine)</td>
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<table>
<thead>
<tr>
<th>MAP due to a decrease in CO and or TPR solely due to abrupt withdrawal of sympathetic nerve traffic to the heart and blood vessels and an increase in cardiac vagal outflow</th>
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<tbody>
<tr>
<td>Neurogenic syncope; aka. neurally mediated syncope (NMS); commonly known as vasovagal syncope, emotional faint</td>
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<tr>
<th>MAP normal; syncope due to paroxysmal increase in cerebral vascular resistance. The rise in cerebral vascular resistance is demonstrated by transcranial Doppler study of cerebral blood flow velocity.</th>
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</thead>
<tbody>
<tr>
<td>Cerebral syncope</td>
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</table>

39. **What is the typical blood pressure response to immersion of the hand in ice-cold water?**

In the cold pressor test (a test of cardiovascular autonomic function), the subject immerses his/her right hand in ice-cold water at 4°C for 1 min. Diastolic pressure increases by at least 10 mm Hg typically. The afferent pathway is the spinothalamic system, and the increase in diastolic pressure is mediated by activation of sympathetic outflow to resistance vessels. If pain and
temperature sensibility are intact during neurologic exam, the absence of a pressor response suggests a defect somewhere in the sympathetic efferent pathway for the pressor response.

40. You have been running at 5 mph on the treadmill for the past 10 min. Cardiac output has increased from 4 L/min to 6 L/min. How would mean arterial pressure (MAP) have changed from baseline?
An increase in cardiac output does not necessarily mean that MAP increases. It depends on what happens concurrently to TPR. One needs to observe BP as well.

41. Why does prolonged standing motionless increase the likelihood of someone fainting?
Compare standing motionless or passively in a tilt table tilted head-up 70 degrees with contracting your leg muscles voluntarily while you stand. In which instance would you expect venous return to be better? It is when you contract your leg muscles because these contractions pressurize deep veins in the lower limbs and facilitate the flow of blood toward the heart. Competent valves in the veins ensure flow toward the heart.

42. A 2 month old child is diagnosed with an isolated ventricular septal defect at 1-month age. On examination, HR was 130 bpm, pulmonary blood flow was abnormally elevated (2 times normal), and the ratio of pulmonary blood flow (Qp) and systemic blood flow (Qs) was 2 (high). Despite high Qp, pulmonary artery pressure was 40/15 mm Hg corresponding to a mean pulmonary artery pressure of 25 mm Hg (WNL), and mean left atrial pressure was WNL. Given that pulmonary blood flow is elevated, how can a normal mean pulmonary artery pressure be explained?

Given, Qs is normal. Qp is twice normal. Pulmonary artery pressure = 40/15 mm Hg.

Since HR is 140 bpm,
Mean pulmonary artery pressure (MPAP) = pulmonary artery diastolic pressure + 0.4 (pulse pressure in pulmonary artery).

In this case, MPAP ≈ 25 mm Hg. Pulmonary hypertension has been defined as a MPAP > 25 mm Hg at rest, or > 30 mm Hg during exercise.

Qp = [MPAP-MLAP] / PVR. Thus MPAP - MLAP = Qp × PVR. Since MPAP-MLAP is normal, a doubling of Qp can be explained by only a halving of PVR. One can infer from this observation that the pulmonary circulation has the ability to accommodate an increase in flow by dilating.

If an increase in blood flow through an artery causes the artery to dilate, it is called flow-mediated dilation (FMD). It might seem like the opposite of the myogenic mechanism, and flow mediated dilation is a phenomenon that is usually studied in conduit arteries although it has been observed in resistance vessels. The shear stress of flow is transduced by the vascular
endothelium into signals that mediate dilation. One way of clinical assessment of endothelial function in conduit arteries is measuring the change in forearm blood flow in response to an infusion of acetylcholine into the brachial artery. Diminished flow-mediated dilation is an independent prognostic marker of adverse clinical outcomes in a variety of pathologic states.

However, if such a high Qp is left untreated, over a time scale of months to years that varies depending on the magnitude of Qp, hypertrophic changes in the pulmonary resistance vessels progressively cause PVR to rise and permanent pulmonary hypertension invariably develops.

43. The following data were obtained from a 30-year-old healthy adult male participating in a clinical research investigation on therapies for pulmonary hypertension. There was no evidence of an intracardiac shunt or shunt between the aorta and pulmonary arteries.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary artery pressure (PAP)</td>
<td>25/10 mm Hg</td>
</tr>
<tr>
<td>Brachial artery pressure</td>
<td>115/70 mm Hg</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure</td>
<td>5 mm Hg</td>
</tr>
<tr>
<td>Mean right atrial pressure</td>
<td>5 mm Hg</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>5 L/min</td>
</tr>
</tbody>
</table>

Comment on whether systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) are normal, and calculate the approximate ratio of SVR and PVR in this individual.

Since there are no shunts, the systemic and pulmonary circulations are in series and flow through them is the same. Qp = [mean PAP – LAP] / PVR; and Qs = [MAP – MRAP] / SVR

Since there is no shunt, Qp = Qs. Thus, SVR / PVR = [MAP-MRAP] / [MPAP-MLAP]

Where Qp – Pulmonary blood flow; Qs – Systemic blood flow; SVR – Systemic vascular resistance; PVR – Pulmonary vascular resistance; MRAP – Mean right atrial pressure; MLAP – Mean left atrial pressure

MAP = DP + 1/3 (PP); in this case it is 85 mm Hg; MPAP = DP + 1/3 (PP) in the pulmonary artery; in this case it is 15 mm Hg

One cannot come retrograde via the mitral valve into the left atrium and then into pulmonary veins. When high fidelity pressure data from the left atrium are required, the left atrium needs to be entered via a probe patent foramen ovale, and then one will need to go back into a pulmonary vein. If there is not a PFO, then an atrial septal puncture is required to enter LA, and then to go back. Thus, normally, pulmonary capillary wedge pressure is used as a surrogate of left atrial pressure or left ventricular end-diastolic pressure. Substituting the values provided, we get SVR/PVR = 8.
Normal reference ranges for PVR and SVR (in any unit) need not be memorized since if blood pressures, Qs and Qp are known, resistance can be readily calculated. By assessing whether MAP, MPAP, Qp and Qs are normal, one can assess if SVR and PVR are normal. Assessing if the absolute value of SVR and PVR are normal is more important. The ratio SVR/PVR does not add any clinically relevant information not obtained by interpreting the component absolute values. Just note from this example that typically, the ratio of SVR/PVR is about 5-10 (roughly the same as the ratio of MAP and MPAP), and that the pulmonary circulation is a relatively low resistance and hence low pressure system.

44. Austin is a 3-year-old baby with an Hb of 12 g/dL. Mixed venous blood obtained from the right ventricle is 75% saturated with oxygen. Would she be expected to be cyanosed on clinical examination?

Cyanosis is clinically apparent when the concentration of deoxyhemoglobin exceeds 5 g/dL. With a total Hb of 12 g/dL that includes 3 g/dL of deoxyhemoglobin in venous blood, Austin would not be expected to have central cyanosis (see definitions below). Peripheral cyanosis may still occur. The key distinction between central and peripheral cyanosis is arterial oxygen tension is low in central cyanosis and is normal in peripheral cyanosis. Clinically, central cyanosis should be sought in vascular beds with lower vasoconstrictor tone such as tongue, gums and buccal mucosa, not the hands, feet or perioral region. Peripheral cyanosis or acrocyanosis (cyanosis limited to the extremities), in contrast, is usually related to reduced blood flow to the skin in the extremities due to vasoconstriction. This is described with exposure to cold, and in patients with severe heart failure, circulatory shock, or peripheral vascular disease.

45. How does squatting relieve cyanotic spells in children with tetralogy of Fallot?

Squatting episodes have been observed to improve oxygenation and relieve cyanotic spells in children with Tetralogy of Fallot. Squatting increases SVR (which is mainly due to resistance of small arteries and arterioles and not venular resistance) presumably due to compression of vessels by contracting muscles. This increases the afterload for the LV, which then generates a higher systolic pressure. The higher LV systolic pressure minimizes the right-to-left shunt, improves pulmonary blood flow and thereby oxygenation of blood. The effects of squatting on venous return are complex – it depends on the duration of the squat. For the first few seconds, squatting pressurizes veins from without resulting and may result in a transient increase in venous return but venous return does not improve any further. In any case, an increase in venous return to the right ventricle will likely increase the right-to-left shunt if at all; i.e., by itself it cannot relieve cyanosis unless SVR is increased.

46. In a normally developed fetal heart, which of the two ventricles works the most? Explain.

In a normally developed fetal heart, the right ventricle works harder than the left, pumping about 55% of the ‘combined cardiac output’. The RV faces two resistors – the much elevated PVR in the collapsed lungs, and SVR. In contrast, the left ventricle is up against only SVR. This is in contrast to what normally happens in postnatal life wherein PVR is typically 5-10 times lower than SVR, and the left ventricle does much more work than the right ventricle.
47. In terms of the “purpose” of the cardiovascular system, which is to oxygenate blood and supply oxygen and energy substrates to tissues and clear them of products of metabolism, what problems do you expect a ventricular septal defect to cause in fetal life? Explain. The ventricles would have to overwork to achieve a given ‘combined cardiac output’ into the aorta. Consider just a ventricular septal defect in fetal life and that all other aspects of development of the heart are normal. This would result in a right-to-left shunt, shunting blood into the left ventricle. The shunted blood would eventually be pumped into the aorta. In the normal case, blood from the right ventricle would reach the aorta via the ductus arteriosus. If the ‘combined cardiac output’ were adequate, this in itself wouldn’t be expected to adversely affect perfusion of the placenta and other fetal tissues.

48. Greg Thomas is a 30-year-old athlete training regularly since the past 5 yr. His resting HR is 40 bpm, and his maximal cardiac output is 25 L/min. In contrast, John Fisher, 30 yr old, leads a much more sedentary lifestyle and has a resting HR of 80 bpm and a maximal cardiac output of 15 L/min. Despite having a low resting HR, how are athletes typically able to achieve a higher maximal cardiac output? Well-trained athletes have a higher cardiac reserve because they have a higher HR reserve and a higher SV reserve. Maximal HR is the same regardless of training. An athlete with a resting HR of 45 bpm can raise it potentially to 180 bpm during intense exercise. In contrast, an individual with a resting HR of 90 per minute can increase it only two fold. At rest and even during exertion, athletes achieve a given cardiac output with a lower HR, compared to controls. This is because athletes also have larger hearts. Physiologic cardiac hypertrophy allows a greater increase in SV via an increase in LVEDV as well as a decrease in LVESV. As a result, athletes have a higher cardiac reserve and can increase their cardiac output typically to about 25-30 liters per minute.

49. An individual with a lower than normal cardiac output may not necessarily be symptomatic at rest. Why is this so? Systemic oxygen delivery (DO₂) = Cardiac output × oxygen concentration of arterial blood

Consider an adult male weighing 70 kg at rest; whole body oxygen consumption at rest is about 250 ml/min. If blood Hb level and oxygen saturation of hemoglobin were normal and oxygen content of arterial blood is 200 ml/L, a cardiac output of 5 liters per minute delivers 1000 ml of oxygen per minute, 4 times the amount of oxygen consumed at rest. There is a considerable reserve with this arrangement. However, with exertion, symptoms are more likely as total DO₂ may not meet the increased demand. Thus some patients with hypovolemia, anemia, heart failure, pulmonary disease are asymptomatic at rest. A reduction in exercise capacity or tolerance should cause one to investigate all factors affecting DO₂ – not just cardiac function, and dyspnea is not specific for heart failure.
50. A healthy adult male assumes the upright posture while being immersed in water up to the neck. What effect would you expect this have on venous return (in comparison to an individual standing upright but not immersed in water)? Explain.
Immersion in water up to the neck minimizes the effect of 1g acting head-to-foot, so venous return increases (relative to that with 1 g).

51. Sometimes neurosurgical procedures are performed with the patient seated. What is the most feared hemodynamic complication in this setting?
Pressure in the venous sinuses in the brain is negative with respect to atmospheric pressure. If a venous sinus is inadvertently opened, it can suck air in, and this can result in ‘air embolism’.

52. You suspect that an individual has right heart failure but at the time of physical examination, the individual is asymptomatic, and JVP measures 8 cm blood (normal: 8 cm blood) from the right atrium. Is there a way of noninvasively checking for the possibility of right heart failure in this instance?
Check for hepatojugular reflux (not reflex). With the subject positioned appropriately for examination of JVP, exert firm pressure in the right upper quadrant for 10-20 seconds. The increase in venous return this causes can overload a failing right heart, and this may be apparent as a rise in JVP.

53. Heart failure is a hypervolemic state. True / False.
This statement raises the question as to what volume is being referred to. Is it total blood volume or ECF volume or effective arterial blood volume? Heart failure is often spoken of as a hypervolemic state and this is evident from manifestations such as pedal edema, congestive hepatomegaly etc. Total blood volume and total ECF volume and total body sodium are all increased. However, the fact that effective arterial blood volume (volume of blood contained in the arterial system) is lower than normal in heart failure should not be forgotten because this is the volume that is available in the service of tissue perfusion.

54. What is the mechanism of edema in congestive heart failure?
By definition, in right heart failure, right atrial pressure is increased. And by definition, in left heart failure, left atrial pressure is increased. In left ventricular failure, the pulmonary veins and capillaries track LVEDP.

In right ventricular failure, congestive hepatomegaly, sacral edema, and pedal edema are a consequence of systemic capillaries tracking (or reflecting) raised right atrial pressure, while arteriolar tone is raised.
Right atrial pressure is the sink for systemic venous return. When the right heart fails as a pump, steady state right atrial pressure increases. This reduces the driving pressure for systemic venous return. In other words, resistance to systemic venous return is increased. Venous return reduces; the result is that more blood pools in compliant systemic veins. Systemic venous pressure increases (venous hypertension).
When systemic venous blood volume approaches the capacitance limit of veins, the resistance of venules is overcome and the high venous pressure is transmitted retrograde to raise capillary hydrostatic pressure. Patients with heart failure also have reflex arteriolar constriction, and thus, capillary hydrostatic pressure ‘tracks’ venular pressure. When fluid efflux from capillaries exceeds drainage by lymphatics, edema results. Since venous pressure is highest in the feet in the upright posture (because of the effect of gravity on hydrostatic pressure), it is readily manifest there.

The second mechanism contributing to edema is renal retention of salt and water. In heart failure, renal hypoperfusion sets up cascades that lead to retention of salt and water. It is important to note that the presence of pedal edema is not diagnostic of heart failure. It may occur, for example, in individuals with renal failure who have volume overload as a result without a primary disease of the heart. If volume overload is corrected by diuresis or dialysis, the edema resolves.

55. **If we diurese a patient with heart failure with a diuretic, where are we first removing fluid from - systemic arteries or systemic veins?**

It is from the arterial system that salt and water is first removed. Is this not inappropriate given that effective arterial blood volume is already reduced in heart failure? Activation of the renin-angiotensin system and an increase in sympathetic outflow is homeostatic in the context of a low cardiac output (due to hemorrhage, hypovolemia, and hypotension) in that it would potentially allow cardiac output and BP to be maintained in the face of a fall in cardiac output by causing vasoconstriction. Why do we then prescribe angiotensin converting enzyme inhibitors for heart failure patients? Indeed, ACE inhibitors are the cornerstone of therapy for the typical patient with heart failure.

If the primary abnormality were a decrease in cardiac output due to a decrease in stroke volume, a reflex increase in heart rate would appear to be a homeostatic response. What is the pathophysiological justification, then, for the use of beta-adrenoceptor blockers, which reduce heart rate and myocardial contractility, for certain subsets of patients with heart failure? I leave this as an exercise for you to attempt. You may find details in the chapter discussing the pathophysiology of heart failure in *Lilly* and in your pharmacology readings of management of heart failure.

56. **Is it possible that an individual with heart failure not have pedal or sacral edema or pulmonary edema? Explain.**

According to Starling’s equation summarizing the role of various forces affecting fluid exchange across capillaries:

\[
\text{Fluid movement} = K_f \left[ (P_c + \pi_i) - (P_i + \pi_c) \right],
\]

where

- \(K_f\) = capillary filtration coefficient
- \(P_c\) = Hydrostatic pressure in the capillaries
- \(P_i\) = Hydrostatic pressure in the interstitium
- \(\pi_c\) = capillary colloid osmotic pressure
¶I = colloid osmotic pressure in the interstitium

Individuals with low cardiac output heart failure who only have ‘forward’ heart failure may not have edema if MAP and therefore systemic capillary hydrostatic pressure is low. Edema occurs when heart failure has progressed to cause retrograde transmission of pressures to pulmonary and or systemic veins (*backward heart failure*). However, with diminished renal blood flow, salt and water retention by the kidneys also contributes to the edema of heart failure.

57. **Why are astronauts positioned supine and chest-to-back when taking g-forces of a spaceflight?**

Begin watching this clip at 3 min [http://www.youtube.com/watch?v=NsmW_y04z_Y](http://www.youtube.com/watch?v=NsmW_y04z_Y) Note astronauts (head-foot) are at right angle to acceleration, and high g acts chest to back. Tolerance for g forces exerted across the body is much better than those exerted head-foot or foot-head. Humans tolerate 11 g acting in a back to chest direction for 3 min, and 17 g acting in a chest to back direction for 4 min.
Multiple-Choice Questions for Self-Assessment

In each of the following questions, select the single best response.

1. Activation of beta-adrenergic receptors in the heart is normally associated with which of the following?
   A. Decrease in the slope of phase 4 depolarization in SA nodal cells.
   B. Decrease in conduction speed through AV node.
   C. Inhibition of Ca induced Ca release following depolarization in ventricular myocytes.
   D. Accelerated sequestration of Ca in the sarcoplasmic reticulum by the Ca-ATPase
   E. Reduction in the rate of rise in ventricular pressure during isovolumic contraction

2. Normally, in postnatal life, the left ventricle is more vulnerable to ischemia and infarction compared to the right ventricle because
   A. diastolic pressure is comparable in both ventricles
   B. pulmonary vascular resistance is greater than systemic vascular resistance
   C. the left ventricle pumps much more blood than the right ventricle
   D. left ventricular subendocardial perfusion is limited to ventricular diastole
   E. flow through the right ventricle is largely passive

3. A 2-month-old child is brought to your office with symptoms suggestive of a respiratory tract infection and a history of poor feeding. On examination, a continuous murmur is heard in the left infraclavicular region but it is loudest during systole. There is no cyanosis. Peripheral arterial pulses are bounding. This clinical finding should cause you to suspect which of the following?
   A. Atrial septal defect
   B. Ventricular septal defect
   C. Patent ductus arteriosus
   D. Mitral regurgitation
   E. Pulmonic stenosis

4. Which of the following is least likely in an individual with chronic severe stenosis of the aortic valve?
   A. Left ventricular hypertrophy
   B. Normal VO2 max
   C. Ejection systolic murmur in aortic area
   D. Proneness to syncope
   E. Soft second heart sound

5. Which of the following is least likely as a mechanism for chest pain in an individual with established aortic stenosis, left ventricular hypertrophy associated with a reduction in ventricular cavity radius, and no angiographic evidence of stenosis of epicardial coronary arteries?
   A. Decrease in diastolic pressure in aorta
   B. Increase in coronary vascular resistance
   C. Increased myocardial oxygen demand
   D. Increase in left ventricular end diastolic volume

6. If a healthy adult human is made to sit in a human centrifuge and subjected to a force equal to + 3 g (i.e., 3 times gravity) for 30 seconds, it is least likely to result in:
   A. a decrease in cerebral blood flow
   B. a decrease in mean arterial pressure
   C. an increase in plasma brain natriuretic peptide
   D. an increase in plasma level of renin
   E. an increase in sympathetic outflow to heart

7. Palpable enlargement of the liver in an individual with heart failure is most closely related to:
   A. a decrease in pulmonary venous pressure
B. an increase in left ventricular compliance
C. an increase in mean arterial pressure
D. an increase in mean right atrial pressure
E. an increase in systemic vascular resistance

8. In postnatal life, steady state outputs of the right and left ventricles are matched in vivo by:
A. matching the tension generated by each ventricle
B. sympathetic influences on the SA node
C. the Frank-Starling mechanism
D. vagal influences on the SA node
E. varying the afterload for each ventricle

9. A 35-year-old man has had worsening shortness of breath for the past 3 years. He now has to sleep with his head rested on two pillows in order not to be breathless. He has no history of chest pain. A month ago, he had a stroke; now he has difficulty moving his left leg and left arm. He is afebrile. Brachial artery BP is 110/70 mm Hg (sitting, in both arms). Auscultation reveals a mid-diastolic murmur in the apex, best heard during expiration with the patient in the left lateral position. Echocardiogram reveals a normal left ventricular diameter and an increase in left atrial diameter. This information is most consistent with which of the following diagnoses?
A. Essential hypertension
B. Mitral stenosis
C. Aortic stenosis
D. Coarctation of aorta
E. Aortic regurgitation

EKG showed normal sinus rhythm throughout. There was no blood loss or injury as a provocative factor, and this gentleman was known to be in good health with no history of heart disease. Syncope in this individual is most likely due to:
A. an increase in systemic vascular resistance
B. atrioventricular dissociation
C. abrupt withdrawal of sympathetic outflow to resistance vessels
D. obstruction to ventricular filling
E. decrease in cardiac vagal outflow

10. The BP and HR of a 24 year old man fell from 120/80 mmHg and 70 bpm to 70 mm Hg (systolic), and 50 bpm respectively over 2 min while he was standing passively in a tilt table tilted head-up right 70°. With this drop in pressure he passed off for nearly 30 seconds before regaining consciousness.

11. Which of the following statements best describes the consequences of arrangement of the systemic and pulmonary circulations in series rather than in parallel?
A. Increasing oxygen concentration of arterial blood is the only means to meet an increase in oxygen demand.
B. The arrangement of systemic and pulmonary circulations in series is energetically wasteful.
C. Cardiac output of the systemic and pulmonary circulations is uncoordinated.
D. Increase in demand for oxygenated blood can be matched by an increase in cardiac output.

12. Normally, which of the following events in the cardiac cycle occurs at some point between S1 and the following S2?
A. Onset of ventricular diastole
B. Atrial systole
C. Rapid ventricular filling
D. The ‘a’ wave of the JVP
E. The ‘y’ descent in the JVP

13. Clinical examination of a 50 year old man reveals splitting of the second heart sound as A2 followed by P2 during deep inspiration, and the split was not apparent during expiration. S1 is normal in intensity, and there is no cardiac murmur. BP is 130/80 mm Hg and pulse is 80 bpm and
regular. Which of the following is the most likely cause of this pattern of splitting of the second heart sound?
A. Aortic regurgitation
B. Left bundle branch block
C. Physiologic splitting of S2
D. Pulmonic stenosis

14. Results of cardiac catheterization in a 50-year-old man who presents with a history of acute breathlessness since the past 8 hours are as below. Coronary angiography showed no evidence of significant narrowing of the right or left coronary arteries or its branches. Saturation (Sat) below indicates percentage saturation of hemoglobin with oxygen.

<table>
<thead>
<tr>
<th></th>
<th>mean RAP 5 mm Hg</th>
<th>PCWP 25 mm Hg</th>
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<tbody>
<tr>
<td></td>
<td>Sat: 75%</td>
<td>Sat: 93%</td>
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<tr>
<td></td>
<td>(normal)</td>
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<td>RV: 2/5 mm Hg</td>
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<td></td>
<td>Sat: 75%</td>
<td>(normal)</td>
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<td>LV: 10/30 mm Hg</td>
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<td></td>
<td>Sat: 92%</td>
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<td>PA: 25/10 mm Hg</td>
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<td>Sat: 75%</td>
<td>(normal)</td>
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<td>Aorta: 100/60 mm Hg</td>
<td>Sat: 92%</td>
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This data is most consistent with the possibility of which of the following as the underlying cause of breathlessness?
A. Tricuspid stenosis
B. Pulmonary stenosis
C. Mitral regurgitation
D. Aortic stenosis
E. Tricuspid regurgitation

15. In the systemic circulation, the highest percentage of blood volume is normally present in:
A. aorta
B. small veins
C. superior and inferior vena cava
D. systemic capillaries

16. Your patient is a 65-year-old man complaining of chest pain and dyspnea on exertion since the past 2 years. He is known to be hypertensive since the past 10 years but has taken medication irregularly. There is no history of syncope. On clinical examination, he is conscious, well oriented, and asymptomatic at rest. BP: 140/90 mm Hg; pulse: 80/min, regular; JVP - normal; and respiration: 16/min. There is no cyanosis, pedal edema or anemia.

Precordium: A loud ejection systolic murmur was heard in the second right intercostal space close to the sternal edge, and radiated to carotid arteries. The same murmur was also heard in the mitral, tricuspid and pulmonary areas. This murmur reduced in intensity during the Valsalva maneuver.

Which of the following is the most likely pathology responsible for this murmur?
A. Aortic stenosis
B. Mitral stenosis
C. Mitral regurgitation
D. Aortic regurgitation

17. Hypocalcemia is associated with QT interval prolongation because it
A. increases the duration of ventricular depolarization
B. it shortens the ST segment
C. it accelerates potassium efflux through inward rectifier potassium (\(K_{ir}\)) channels
D. it increases cytosolic calcium
E. lengthens the duration of ventricular repolarization

18. The figure below shows two ventricular performance curves. Identical volumes of isotonic NaCl were administered starting at the point at which the arrows are pointing below.
Based on this information one can conclude that:
A. curve B represents that of a failing heart
B. curve A is that of a failing heart
C. curve A is associated with a more favorable response to fluid therapy
D. curve B is that of a heart whose contractility is reduced.

19. In clinical practice, arterial BP is routinely measured in the brachial artery held at the level of the heart because
A. the hydrostatic pressure in the brachial artery pressure is the same as the hydrostatic pressure in most systemic arteries
B. it is the only systemic artery at the same hydrostatic level as the heart
C. the measured diastolic pressure is independent of lower limb vascular resistance
D. the measured pulse pressure is independent of large artery compliance
E. the measured systolic pressure is often a surrogate of left ventricular systolic pressure

20. Electrical activity in which region of the heart does not result in deflections on the surface electrocardiogram?
A. Atria
B. Bundle of His
C. Free wall of the left ventricle
D. Free wall of the right ventricle
E. Muscular portion of the ventricular septum

21. If net QRS deflection is equiphasic (or null) in lead aVF and tallest and upright in lead I, the mean electrical axis of the QRS vector in the frontal plane is about
A. – 30 degrees
B. 0 degrees
C. + 30 degrees
D. + 45 degrees
E. + 90 degrees

22. In which of the following leads are you most likely to observe ST segment elevation when there is an acute and extensive infarction of the anterior and lateral wall of the heart?
A. Leads I, II and III
B. Leads aVR, aVL and aVF
C. Leads I, aVL, and V1-V6
D. Leads II, III and aVF

23. In which of the following states is isovolumetric ventricular relaxation abbreviated, assuming that the prevailing heart rate is identical in each?
A. Aortic regurgitation
B. Mitral regurgitation
C. Mitral stenosis
D. Tricuspid regurgitation
E. Patent ductus arteriosus

24. Which of the following has a direct vasodilator effect on smooth muscle in arterioles in the presence of endothelial dysfunction?
A. Acetylcholine
B. Angiotensin II
C. Nitric oxide
D. Norepinephrine
E. Thromboxane A2
25. Plasma level of brain natriuretic peptide is **least likely** to be elevated in:
A. acute mitral regurgitation
B. cardiac tamponade due to chest trauma
C. heart failure due to dilated cardiomyopathy
D. heart failure due to acute aortic regurgitation
E. heart failure post myocardial infarction

**Answers & Explanations:**

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1. *Beta*-adrenergic receptor activation in the SA node increases the slope of phase 4 depolarization in SA nodal cells, thereby increasing SA nodal firing rate. Conduction speed through AV node increases. Calcium influx ($I_{Ca}$) and calcium induced calcium release are facilitated. Sequestration of Ca in the SR is enhanced; this is how it accelerates myocardial relaxation. Remember, an increase in HR entails an acceleration of the rate of contraction as well as relaxation. The rate of pressure increase during isovolumetric ventricular contraction is increased because of enhanced calcium influx and an increase in sensitivity of contractile proteins to calcium (*positive inotropic effect*).

2. D is true. LV systole compresses the branches of coronary arteries perfusing the LV. In contrast pressure in the RV is lower than the pressure in the coronary artery throughout the cardiac cycle.

3. The murmur of patent ductus arteriosus is continuous (heard throughout the cardiac cycle) because the gradient driving flow from the aorta to the pulmonary artery exists throughout the cardiac cycle. Since there is no cyanosis, the shunt is left-to-right. In PDA, a considerable fraction of left ventricular cardiac output is shunted through the pulmonary circulation and it volume overloads the left heart. (Lilly, p. 374).

4. Aortic stenosis represents a relatively constant increase in LV afterload. Despite left ventricular hypertrophy, maximal cardiac output and maximal oxygen uptake (VO2 max) is diminished reducing exercise capacity.

5. The reduction in ventricular cavity diameter and the increase in ventricular stiffness due to interstitial fibrosis would reduce EDV if at all.

9. In isolated mitral stenosis, LV radius is normal; the increase in LA diameter is reflective of the MS. There is no reason for systemic BP to be abnormal in the absence of some other pathology. The murmur is typical. The stroke would most likely have resulted from thromboembolism, a complication of atrial fibrillation. The left atrial dilation in MS is a substrate that fosters the development of atrial fibrillation.

10. The description in the question is that of an individual with vasovagal syncope characterized by abrupt arteriolar dilation and bradycardia (HR < 60 bpm). Abrupt arteriolar dilation has been shown to be due to an abrupt decrease in sympathetic outflow to resistance vessels, and the bradycardia is due to an increase in cardiac vagal outflow. *Option A* – an increase in SVR is incorrect because BP dropped to a very low value. *Option B* – AV dissociation is incorrect because the EKG rhythm is mentioned to have been sinus throughout. *Option D* – there is no evidence of obstruction to ventricular filling (such as occurs in pericardial tamponade). *Option E* – an abrupt increase in cardiac vagal outflow...
underlies the bradycardia.

12. Ventricular relaxation commences and ventricular pressure begins to fall before the aortic valve snaps shut (S2). Options B and D, atrial systole (a wave) occurs just prior to S1. Rapid ventricular filling commences after S2. Option E - the ‘y’ descent of the JVP represents the fall in atrial pressure during ventricular filling and occurs between S2 and S1.

13. See Lilly, pp. 33-34 for a discussion.

14. There is evidence of LV failure (high LVEDP); this is the cause of the high PCWP. An LVEDP > 12 mm Hg is elevated. Pressure gradients across valves are normal. There is no evidence of an intracardiac shunt. Of the options given, the only possibility is mitral regurgitation. A patient with acute mitral regurgitation, such as due to papillary muscle infarction, may present with acute pulmonary edema.

16. Aortic stenosis. What is uncommon with isolated aortic stenosis is a pulse pressure of 50 mm Hg, because the stroke volume in isolated AS is low and therefore the pulse pressure is typically lower than 40 mm Hg. The patient is 65 years old and likely has systemic hypertension and atherosclerotic changes in large arteries that explain the high pulse pressure – they may be due to diminished arterial compliance. In contrast, the loud ejection systolic murmur heard best in the second right intercostal space and conducted to the carotids is indicative of aortic stenosis. How hemodynamically significant the stenosis is, will of course, need to be evaluated. Option B – mitral stenosis would produce a mid-diastolic murmur best heard in the apex with the breath held during expiration. Option C – mitral regurgitation would produce a holosystolic murmur heard best in the apex. Option D – isolated aortic regurgitation would produce an early diastolic murmur heard best in the lower left sternal edge and the apex.

18. There are no numbers on the x- or y-axis so we can't comment on whether curve A or B is that of a failing heart. All that we can do with this graph is compare their responsiveness to volume loading, and curve A represents a relatively greater increase in SV with an increase in preload. Option D is incorrect since a lower SV for the same preload can be a result of one of two things: lower myocardial contractility, or higher afterload. We don't have sufficient information in the question to distinguish between these two possibilities.

Option A is incorrect. In someone in the upright position, hydrostatic pressure varies from region to region because of the effect of gravity. The pressure driving blood flow in the arteries (driving pressure, a dynamic component of pressure) is what we are seeking to measure when we typically measure arterial pressure (we don't want the readings to be influenced by hydrostatic effects). One reason we measure it in the brachial artery, it is the only one that can be conveniently positioned at the same hydrostatic level as the heart for a noninvasive BP recording. Option B is false; parts of the aorta are at the same level as the heart. Option E is true, discussed in Question 21, on p. 10.

20. Electrical activity in the AV node and bundle of His are not strong enough to produce deflections on the surface ECG. One can however record an ECG with electrodes close to the tricuspid valve (His Bundle Electrogram), and also simultaneously record the surface ECG.

21. This is testing knowledge of the hexaxial
reference system and two basic principles of electrocardiology. See Lilly, pp. 87, 89-91.

23. Regurgitation through aortic valve causes ventricular filling during what would normally have been isovolumetric ventricular relaxation.

24. When there is endothelial dysfunction, NO which physiologically originates from endothelial cells is limiting. However, drugs that are broken down to release NO (example, nitroglycerin) can still induce some dilation in the presence of endothelial dysfunction. See Boron, p. 499. This is called endothelium independent vasodilation. However for acetylcholine to have a vasodilator effect, an intact endothelium is required.

25. BNP is released in response to abnormal stretch (increased passive tension) of ventricular myocytes such as in heart failure. In tamponade, the increase in ventricular diastolic pressure is because of compression by high intrapericardial pressure rather than increased stretch of ventricular myocytes.
References:


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ACCF/AHA Guidelines on the Management of Heart Failure (2013). *Circulation*, 2013 published ahead of print: http://circ.ahajournals.org/content/early/2013/06/03/CIR.0b013e31829e8776.citation


