Anesthetic Pharmacology: Physiologic Principles and Clinical Practice: Control of Blood Pressure and Vascular Tone:

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Primer: Minimum essential information that an anesthesiology trainee should retain from this chapter.

1. Factors involved in the control of the blood pressure and vascular tone.
    a. Vascular mechanics
    b. Autonomic function
    c. Hemodynamics
    d. Ventricular function
    e. Efficient Ventricular Function and the Vasculature
    f. Heart Rate
2. Pharmacology
3. How do you solve hemodynamic problems?

The pharmacologic control of blood pressure and vascular tone can be addressed using a number of approaches. The choice of an inotrope or vasoactive compound should be based on an understanding of the cardiovascular system, the cause of the hemodynamic perturbation being treated, and the pharmacology of the agent. The appropriate management of hemodynamic perturbations must be based on a guess at the etiology of the hemodynamic perturbation, the pathophysiology of the patient, the pharmacology of the pharmacologic agents, and how these factors interact. This chapter will discuss the physiologic and pharmacologic factors that go into the choice of inotropes and vasoactive compounds. The response to a pharmacologic agent is a complex combination of the direct pharmacologic actions, the hemodynamic response, and the autonomic response. There are a set of basic anatomic and physiologic functions that must be understood in order to master hemodynamics and to allow the diagnosis and optimal treatment of hemodynamic problems. This chapter will briefly review hemodynamics, autonomic control, cardiac physiology including ventricular function and ventricular energetics, and then the pharmacology of inotropes, vasocontrictors, vasodilators, and their use to control blood pressure and vascular tone.

The cardiovascular system, because of the Frank-Starling mechanism, is inherently stable. The distribution of blood between the pulmonary and systemic circulations is maintained without any outside inputs.[1] The preload dependence of cardiac output, which is defined by the Frank Starling mechanism, makes the relative distribution of pulmonic and systemic blood volumes inherently stable and is controlled by ventricular mechanics. Unfortunately, hemodynamic perturbations, either from changes in blood volume, positional changes of the patient, or vasodilation of vascular beds as metabolic

requirements change, are not handled well solely by the Frank-Starling mechanism of the heart. As vascular beds vasodilate in response to changes in metabolic load, or venous beds dilate, or blood volume changes in response to hemorrhage, cardiac output and blood pressure change without the control of the autonomic nervous system. The autonomic nervous system controls vascular tone, which effects both systemic vascular resistance and venous capacity,[2] the relative distribution of blood flow to organs, and the inotropic and chronotropic state of the heart. The combination of an inherently stable cardiovascular system combined with a control system based on the autonomic nervous system, makes a very stable hemodynamic system. Patients are able to change their position in gravitational fields (an example would be standing up), exercise, and have acute changes in blood volume with relatively minor changes in blood pressure and cardiac output, because of the combination of the inherently stable cardiovascular system and regulation by the autonomic nervous system.[1,3,4]

Anesthesia and many medications administered to patients inhibit the autonomic nervous system and reduce hemodynamic stability. The entire point of anesthesia is to reduce the body's response to surgical stimuli. Suppressing autonomic response is a fundamental component of anesthesia. Anesthetics inhibit the heart rate and blood pressure response to pain.[5] When patients undergo general anesthesia, the systemic vasculature vasodilates, decreasing systemic vascular resistance, venous capacity vessels dilate, reducing central venous pressure and venous return, filling pressures drop, blood pressure drops, and breathing frequently stops. Vasodilation in response to anesthesia, is sufficient to drop the core temperature by vasodilating the skin causing a redistribution and mixing of peripheral and central blood volumes.[6] General anesthesia inhibits the

autonomic nervous system reducing or eliminating the autonomic control of blood pressure and heart rate.[7] Heart rates, in response to synthetic opioid (fentanyl, sufentanil, remifentanil, etc) stimulation of vagal reflexes, may become profoundly bradycardic (HR = 30's to 40's).[8] Sufentanil can increase vagal effects to the point of asystole.[9] The carotid baroreceptor reflexes are inhibited by anesthesia.[10] One of the major goals of anesthesia is to reduce autonomic response to painful stimuli. Unfortunately one result of anesthesia inhibiting the autonomic nervous system is a less stable hemodynamic system in response to vasodilation, changes in blood volume, changes in patient position, changes in temperature, hypoxia, or pain. The anesthesiologist becomes the "autonomic nervous system" for the patient under general anesthesia. The anesthesiologist is responsible for taking over the function of the autonomic nervous system and for maintaining blood pressure, cardiac output, blood volume, temperature, bladder function, respiration, and other autonomic functions.

Autonomic Nervous System:

Closed loop control based on measurement of blood pressure by the baroreceptors, and regulation by the sympathetic and parasympathetic nervous systems, maintains blood pressure in response to changes in blood volume, metabolic demand, and vasodilation. Anesthesia inhibits the autonomic nervous system reducing the efficacy of this control system making the system less stable. The autonomic nervous system is divided into sympathetic and parasympathetic systems (see Fig XX in Chapter 23). Parasympathetic efferents (outputs) arise from the dorsal motor nucleus of X and form into the vagus nerve.[11] The most common vagal effect on hemodynamics, is slowing of the heart in response to vagal stimulation. One of the more common hemodynamic perturbations

caused by the parasympathetic nervous system is fainting from vasovagal effects. This reflex can be quite profound during ophthalmic surgery with the occulocardiac reflex causing brief asystole. The most common autonomic effects of the sympathetic nervous system in anesthetic care, are either vasodilation in response to inhibition of sympathetic tone with induction of general anesthesia, or tachycardia and hypertension with sympathetic stimulation in response to pain. The hypertensive and tachycardiac response of the sympathetic nervous system to surgical stimulation is used to monitor depth of anesthesia. Autonomic control of the cardiovascular system relies on multiple pressure sensors and output control systems. Sympathetic afferents arise from the carotid sinus baroreceptors and form into the carotid sinus nerve, then form the glossopharyngeal nerve and synapse in the nucleus tractus solitarius (NTS) in the medulla oblongata.[12] There are also afferent sympathetic nerves (inputs) from the aortic arch, right atrium, left atrium, and pulmonary artery and venous baroreceptors.[13-16] Projections then go from the NTS to the dorsal motor nucleus of X[17] and the intermediolateral column.[18] Sympathetic efferents from the intermediolateral column synapse in the sympathetic chain ganglion prior to sending efferents to the blood vessels to control systemic vascular resistance and venous capacity. Sympathetic efferents also project to the heart to control inotropic state. Figure 1 shows a system diagram for autonomic control of hemodynamics. The NTS compares the pressure measured by the baroreceptors to a set point, and sends signals to the dorsal motor nucleus of X for parasympathetic outputs,[17] and the intermediolateral column[18] which controls sympathetic outputs, which combine to control the cardiovascular system. Intermediolateral column nuclei are predominantly in the thoracic cord (T1-T12) with cardioaccelerator fibers from T1-T5. The output of the

cardiovascular system (blood pressure) is then detected by the baroreceptors and fed back to the NTS.[12] Closed loop control based on measurement of blood pressure by the baroreceptors and regulation by the sympathetic and parasympathetic nervous systems, maintains blood pressure given changes in blood volume, metabolic demand, and vasodilation. Figure 1 bottom panel shows the complete input and output system. There are multiple interactions between the control systems with carotid reflexes inhibiting many cardiopulmonary reflexes. Figure 2 shows an example of the response curves for the interaction of left and right carotid baroreceptors (RCSP). The use of anesthetics, including local anesthetics placed in the thoracic epidural space, can profoundly inhibit this system.

Hemodynamics:

Hemodynamic instability is common after the induction of anesthesia and can be used to demonstrate the key elements in correcting hemodynamic problems. The first step is to identify the etiology of the problem. Is the etiology vascular volume, systemic vascular resistance, chronotropy (heart rate), inotropy (ventricular systolic function), lusiotropy (ventricular diastolic function), or some extrinsic problem such as tamponade (a lusiotropic problem), or tension pneumothorax (a problem with venous return)? The diagnosis can usually be obtained by a combination of brief history and statistical likelihood among common potential causes. A young patient who just had the induction of anesthesia most likely has a decrease in systemic vascular resistance and venodilation lowering preload. The most common therapy would be an infusion of volume. A previously healthy patient with trauma most likely has a low blood volume. An elderly patient with pre-existing coronary artery disease, who has just had the induction of

anesthesia, may have a low preoperative blood volume and vasodilation. The therapy would be volume and possibly a vasoconstrictor. If the hypotension persists despite first attempts at therapy, other etiologies such as ventricular dysfunction and/or myocardial ischemia need to be addressed. History and statistical likelihood are the first approach. If the first approach at therapy does not work, additional information should be obtained. Therapy should be guided to correct the problem. Vasodilation, blood volume, or cardiac problems should be investigated separately.

Vasodilation causes two problems which should be viewed separately. Arteriolar vasodilation lowers systemic vascular resistance and afterload. Venous dilation dilates systemic veins, increasing their unstressed vascular volume, decreasing central venous pressure, and decreasing preload, which lowers cardiac output. Both changes in systemic vascular resistance caused by arteriolar dilation, and changes in unstressed vascular volume caused by venous dilation, must be addressed when "vasodilation" occurs. Systemic vascular resistance and blood volume must be increased to compensate for "vasodilation".

The next important point to note is that pharmacologic agents have three basic effects. They have the direct effect noted in the package insert on the autonomic nervous or vascular systems. They may also have direct effects on blood vessels and the heart. Finally, the hemodynamic changes may cause reflex effects making the net response even more complex. The combined effect is complex because is it rare that each component can be isolated. For example, inhaled anesthetics inhibit autonomic tone,[5,19] have direct vasodilatory effects,[20] inhibit ventricular function,[21] dilate coronary arteries,[22,23] and may cause sympathetic stimulation through irritant receptors (desflurane[24,25]), all of which

may lead to reflex compensation in response to decreases in blood pressure. The net result of this combination of autonomic, vasodilatory, and cardiac effects is both dose and time dependent and complex to predict in magnitude. A patient with low blood volume may not tolerate the vasodilation following induction of anesthesia. Figure 3 illustrates a fundamentally important concept. Patients with an intact autonomic nervous system can maintain normal blood pressure if blood volume is decreased by 10%.[3,4] At a certain point, further decreases in blood volume result in a decrease in blood pressure. Patients with an inhibited autonomic nervous system (such as those under general anesthesia) decrease their blood pressure with all decreases in blood volume. If a patient is already on the decreasing slope of this relationship, then induction of general anesthesia (with a shift from the solid to the dashed line) may result in dramatic and possibly lethal decreases in blood pressure.

Vascular System:

The most common hemodynamic problems are the result of vascular problems, either blood volume, venous capacity, or systemic vascular resistance. It is very difficult, if not impossible, to have sufficient cardiac function to compensate for a vasculature that is not functioning properly. Profound vasodilation either from anaphylaxis or septic shock can progress to cardiac failure. Rapidly correcting the vascular problem is essential to prevent the progression to cardiac failure. Profound volume depletion will rapidly lead to hypotension, which will result in poor coronary perfusion, myocardial ischemia, myocardial infarction, ventricular stunning, arrythmias, and ultimately cardiac failure. The most common hemodyamic problems are the result of vascular problems, either blood volume or resistance. An example will make the point clearer. Suppose systemic

vascular resistance which is normally 900–1200 dynes·sec/cm^5 (90–120 MPa·s/m^3) is reduced during shock to 400 dynes·sec/cm^5. What would the cardiac output need to be to have a reasonable blood pressure?

$$SVR = \frac{(MAP - CVP)}{CO} * 80$$

Where SVR is systemic vascular resistance, MAP is mean arterial pressure, CVP is central venous pressure, and CO is cardiac output. The 80 converts the units to dynes·sec/cm^5. Rearranging, the cardiac output would be given by

$$CO = \frac{(MAP - CVP)}{SVR} * 80$$

Substituting in SVR = 400 dynes·sec/cm^5 and some typical values (MAP = 60 mmHg, CVP = 10 mmHg), gives a cardiac output = 10 liters/minute! Unless the heart is able to produce a cardiac output of 10 liters/minute, the blood pressure will be quite low. The effect of systemic vascular resistance or afterload on cardiac output requirements is a fundamentally important point. For the heart to work efficiently, the systemic vascular resistance must be reasonable and the blood volume adequate. The first steps in solving hemodynamic problems is to assess blood volume for adequacy and systemic vascular resistance for reasonableness.

Ventricular Function:

The next important point in control of blood pressure and vascular tone is ventricular function. Decisions on hemodynamic management must consider the effects of the pharmacologic agent not only on blood pressure and cardiac output but also on ventricular function, ventricular energetics, oxygen consumption, and efficiency. A brief review of ventricular mechanics and energetics is essential to understand these effects.

There are many different models that have been used to explain ventricular mechanics. The most successful has been the Sagawa model of pressure-volume analysis.[26-28] Pressure-volume analysis plots simultaneously measured pressure and volume data on a single graph. Sagawa, Suga, and Shoukas applied the techniques of pressure-volume analysis used in thermodynamics of engines to the heart.[26] A simple linear relationship was identified between end-systolic pressure and volume. The end-systolic pressure-volume relationship is an afterload independent measure of systolic ventricular function[26] that completely describes the systolic properties of the ventricle.[28] The end-diastolic pressure-volume relationship completely describes the passive diastolic properties of the ventricle. Together the end-systolic and end-diastolic pressure-volume relationships provide a complete description of the mechanical properties of the ventricle. The ventricle operates between the end-systolic and end-diastolic pressure-volume relationships (Figure 4)

Ventricular Function and Energetics:

Pressure-volume analysis also describes myocardial energetics, oxygen consumption, and efficiency.[29] The area of the pressure-volume relationship describes the work performed by the ventricle.[30] The stroke work performed by the ventricle is the integral of pressure with respect to volume integrated from the end-diastolic volume to the end-systolic volume.[31,32]

$$StrokeWork = \int_{EDV}^{ESV} P(v)\,dv$$

The pressure-volume plot of an ejecting beat is shown in Figure 4, where ESV is end-systolic volume and EDV is end-diastolic volume, P(v) is the pressure at a given volume and dv is the change in volume. The grey area is the stroke work for a single

ejecting beat. End-diastolic volume is the lower right corner of the grey area. Tracing around the plot in a counter-clockwise direction starting at end diastole, there is initial isovolumic contraction. When left ventricular pressure exceeds aortic pressure, the aortic valve opens and left ventricular ejection begins. When the pressure in the left ventricle drops below aortic pressure, end-systole occurs, followed by isovolumic relaxation. Once left ventricular pressure drops below left atrial pressure, the mitral valve opens and ventricular filling begins. Stroke volume is the difference between end-diastolic volume and end-systolic volume. The integral of pressure with respect to volume between end-diastole and end-systole represents the work of ejection (gray area in Figure 4).

$$StrokeWork = \int_{EDV}^{ESV} P(v)\,dv$$

Another concept is that of potential energy (Figure 5). Consider an isovolumic non-ejecting beat. If the ventricle is forced to contract without ejecting, it still consumes energy on each beat. In a non-ejecting beat, there is only potential energy of the pressurized ventricle on each beat. No external work is performed because there is no ventricular ejection. The potential energy of the ventricle is given by the area of the black triangle (Figure 5). In a non ejecting beat no external work is done but energy is consumed (Figure 5 top panel). All energy in a non ejecting beat is potential energy of the pressurized ventricle and is given by the area to the left of the isovolumic relaxation line (Figure 5, top panel). In an ejecting beat, there is both potential energy of the pressurized blood at end systole (black triangle) and the external work of the ejected blood (gray square) (Figure 5, bottom Panel).

Ventricular Function and Energetics and Oxygen Consumption:

There is a very close relationship between ventricular energetics described by the pressure-volume analysis and oxygen consumption.[33] Total oxygen consumption per beat can be described by the area between the end-systolic pressure-volume relationship and the end-diastolic pressure-volume relationship for each beat.[34] The total area in figure 6 top panel, which is the sum of the potential energy and the external work, gives the total energy for each beat and the total energy is proportional to oxygen consumption for each beat. The relationship between the pressure-volume area and oxygen consumption per beat can be used to analyze ventricular performance. Prior to doing that, let's derive one more term. The efficiency of ventricular function can be calculated by the ratio of external work divided by total energy consumed per beat.[32] Total work is equal to the total energy consumed per beat and is proportional to the total oxygen consumed per beat. The total energy consumed per beat is equal to the sum of the external work and the potential energy per beat. The efficiency can therefore be derived from the oxygen consumed to pump blood divided by the total oxygen consumed per beat.[32]

$$TotalWork = PotentialEnergy + ExternalWork$$

$$Efficiency = \frac{ExternalWork}{TotalWork}$$

$$Efficiency = \frac{ExternalWork}{ExternalWork + PotentialEnergy}$$

$$Efficiency = \frac{OxygenConsumedtoPump}{TotalOxygenConsumedPerBeat}$$

Pressure-volume analysis allows the rapid evaluation of a complex physiologic system. For example, what are the effects of changing afterload on ventricular energetics? In the standard pressure-volume plot, with external work and potential

energy, total oxygen consumption is the sum of the black and grey areas (Figure 6A (top panel)). The efficiency is the grey area divided by the sum of the black and grey areas. Lets examine the effect of an increase in afterload, such as could be accomplished clinically by administering a vasoconstrictor such as phenylephrine (Fig 6B (middle panel)). Total energy consumption (sum of grey and black areas) is increased, but stroke volume is decreased and cardiac output decreased. The efficiency, as calculated by the ratio of oxygen consumed to pump blood divided by total oxygen consumed, would decrease. Thus administering a vasoconstrictor raised afterload, lowered stroke volume, lowered cardiac output, increased total oxygen consumption, and lowered ventricular efficiency. Conversely, afterload reduction (nitroprusside) would increase both stroke volume and cardiac output, decrease total oxygen consumption, and improve efficiency (Figure 6C (bottom panel)).

Understanding ventricular energetics and ventricular function is important in solving hemodynamic problems. The ventricle works as part of the vascular system. Is it a profound mistake to attempt to solve hemodynamic problems by focusing exclusively on the heart. The heart, while important, is too often viewed as the cause and solution of all hemodynamic problems. Most hemodynamic problems are not primarily cardiac in nature. Most hemodynamic problems are fundamentally vascular problems: systemic vascular resistance, venous capacity, or blood volume. Moreover, vascular problems are extremely common causes of death. For example, hypovolemia is a vascular problem. Inotropic support alone will NOT solve the problem of hypovolemia. The profound vasodilation of anaphylaxis or septic shock is primarily a vascular problem. Tamponade is a vascular problem in that the heart can not fill secondary to decreased diastolic

compliance. Vascular problems frequently lead to low blood pressure, which lowers coronary blood flow, which leads to myocardial ischemia, arrhythmias, and finally death. The primary problem is vascular and the primary solution should be to correct the vasculature.

Impedance and Optimal Hemodynamics:

Optimal vascular function is essential to optimal ventricular performance.[31] The heart fundamentally is a pump that transfers blood from the venous system to the arterial system. In all physical systems including the cardiovascular system, maximal energy transfer of a system is achieved when the output impedance of the source equals the input impedance of the load.[31] Impedance is the opposition of a system to a driving function. In the cardiovascular system vascular resistance is the simplest form of impedance. Impedance matching is the practice of attempting to make the output impedance Z_S of a source, equal to the input impedance Z_L of the load, in order to maximize the power transfer. Impedance matching provides maximal energy transfer between source and load in all physical systems including electrical, mechanical, and hemodynamic.

In the cardiovascular system, impedance matching between the venous system and the heart in diastole, and the arterial system and the heart in systole is essential to achieve optimal energy transfer. [31,35,36] If the afterload is too high, cardiac output is depressed. If the afterload is too low, blood pressure will be two low to maintain coronary perfusion resulting in myocardial ischemia. Afterload describes the impedance of the ventricle in systole and that of the arterial system. Preload is the relationship between the impedance of the venous system and that of the ventricle in diastole. Both

preload and afterload must be optimized to match the venous and arterial systems to the ventricle for optimal performance.

Pressure-Volume Analysis and Impedance Matching to the Vasculature:

Figure 7 (top) gives a schematic of the cardiovascular system. The impedance of the heart can be described by the pressure-volume relationship.[31,32] The end-diastolic pressure-volume relationship describes the input impedance to the heart. The end-systolic pressure-volume relationship describes the output impedance of the heart. The end-diastolic and end-systolic pressure-volume relationships describe the diastolic and systolic elastances of the ventricle. The slope of the ventricular diastolic pressure-volume relationship is about 0.1 mmHg/ml.[10,37,38] The elastance of the venous system is about 0.1 mmHg/ml.[2,15,39] The normal venous system has a very similar elastance to the ventricular diastolic elastance, providing impedance matching between the venous system and the ventricle in diastole.[39] The slope of the systolic pressure-volume relationship normally is about 2.0 mmHg/ml which is very similar to the arterial elastance of 2.0 mmHg/ml, once again matching the output systolic impedance of the heart to the input impedance of the arterial system.[10,37-39] The heart in essence changes it's elastance from that of the venous system (0.1 mmHg/ml) to that of the arterial system (2.0 mmHg/ml) on each beat (Figure 7, middle).[31,35,40] The contraction of the heart can be described as a change in ventricular elastance between the elastance of the venous system and the elastance of the arterial system. If the elastance of the venous system and the diastolic elastance of the heart are equal, there will be maximal transfer of energy from the venous system to the heart (i.e. optimal filling). If the elastance of the ventricle at end-systole

equals that of the arterial system, there will be optimal energy transfer (i.e. optimal ejection).

Hemodynamic Problems and Impedance

Solutions of hemodynamic problems should be thought of as optimizing energy transfer from the venous system to the heart, and from the heart to the arterial system by matching the impedance of the venous system to diastolic impedance of the heart, and optimizing the impedance of the arterial system to the systolic impedance of the heart.[39] Figure 7 (bottom) shows the maximization of cardiac function by matching the arterial elastance E_{EA} to the end-systolic pressure-volume relationship E_{ES}. Maximum cardiac function with minimal energy consumption and maximum efficiency can only be achieved when the venous impedance matches the diastolic elastance and the arterial impedance matches the systolic elastance of the heart.[32,39]

Coronary Perfusion:

It is important to remember that coronary perfusion to the left ventricle occurs during diastole. It is given by: $CBF = \frac{(DBP - LVEDP)}{CVR}$ where, CBF is coronary blood flow, DBP is diastolic blood pressure, LVEDP is left ventricular end diastolic blood pressure, and CVR is coronary vascular resistance. For example, if the diastolic blood pressure decreases from 60 to 45 and the left ventricular end diastolic blood pressure increases from 10 to 20, then coronary perfusion pressure (DBP-LVEDP) decreases from (60-10) = 50 mmHg to (45-20) = 25 mmHg, resulting in a 50% reduction in coronary blood flow. Decreasing diastolic blood pressure by small amounts can have profound implications for coronary blood flow. Appropriate afterload and preload are important to optimal coronary perfusion and ventricular function.

Heart Rate:

There is a very important point to make about heart rate. Figure 8 illustrates the effects of heart rate on coronary blood flow and oxygen demand. Oxygen demand is per beat.[34] Increases in heart rate increase oxygen consumption of the heart.[41] Coronary blood flow to the left ventricle occurs only during diastole. As heart rate increases, the systolic component of the cardiac cycle changes little in duration but the diastolic period shortens, shortening the time for coronary perfusion.[42] Increases in heart rate increase oxygen consumption, while decreasing coronary blood flow and oxygen supply. There is a heart rate in all patients where oxygen supply will be inadequate for demand, resulting in myocardial ischemia. The only question is what is the heart rate for the ischemic threshold? In contrast, increases in blood pressure increase oxygen demand, but they also increase coronary blood flow. There is no threshold high or low blood pressure that is guaranteed to lead to myocardial ischemia. The next point in discussions of heart rate is that the equation $CO = HR * SV$ is misleading. It suggests that increasing heart rate causes an increase in cardiac output. Whether increases in heart rate change cardiac output depend on the initial heart rate, the patient, and the medical condition. There are heart rates that are too low, where increases in heart rate will increase cardiac output. There are heart rates where increasing the heart rate will lower cardiac output, because of inadequate time for diastolic filling. The relationship between heart rate and cardiac output is not highly correlated ($R^2 = 0.29$, $p < 0.0010$) as $CO = HR * SV$ would suggest.[43] The following is true: $SV = \frac{CO}{HR}$; the later $CO = HR * SV$ is not strictly correct.[43]

Pharmacology:

Having established a fundamental understanding of the control of the cardiovascular system including vascular function, cardiac mechanics, and autonomic control, the next objective is to understand how pharmacologic agents can be used to manipulate this system. Table 1 details the mechanism of action and physiologic effects of some of the common pharmacologic agents used to control hemodynamics. In solving hemodynamic problems, the first step is to identify the cause.

1. Volume
2. Systemic Vascular Resistance
3. Pulmonary Vascular Resistance
4. Venous Capacity
5. Inotropic State
    a. Left Ventricle
    b. Right Ventricle
6. Chronotropic State
7. Lusiotropic (Diastolic Function) State
8. Tamponade
9. Tension Pneumothorax

The next step is to fix the identified problem. Identification of the causal problem: volume, resistance, capacity, inotropic state, chronotropic state, lusiotropic state, will suggest possible solutions. The faster the cause of a hemodynamic problem is identified and corrected, the fewer side effects such as myocardial ischemia and ventricular stunning will occur, and the easier it will be to correct the problem. If hemodynamic perturbations can be avoided through prophylactic therapy, the cardiovascular system

will be even more stable. Avoiding a problem is always superior to trying to correct the sequellae of a problem.

Identification of the cause of hemodynamic problems should be done logically. What is the most likely etiology: volume, vasodilation, or ventricular function? If a single intervention does not immediately solve the problem, then additional data should be obtained to identify the cause. If the cause is something other than vascular volume, then a pharmacologic intervention may be needed. The simplest approach is to choose a drug that specifically addresses the problem. It is rare that there is only a single pharmacologic agent that is the correct solution to a hemodynamic problem, rather, there are usually multiple acceptable drugs. There are, however, incorrect choices. If the systemic vascular resistance is low, using a drug that lowers systemic vascular resistance is a mistake (dobutamine, amrinone, milrinone). If the resistance is high, choosing a drug that raises resistance even more (phenylephrine, norepinephrine, epinephrine) is a mistake. If the heart rate is high, choosing a drug that raises it even more (beta agonist) is a mistake. If the afterload is high, lowering afterload will commonly raise cardiac output (Figure 7C). Use of arterial vasodilators such as nitroprusside in the face of elevated systemic vascular resistance will improve ventricular efficiency, and lower oxygen consumption, while raising cardiac output.

Vasoconstrictors and vasodilators:

Management of vascular tone through the use of vasodilators and vasoconstrictors is essential to optimal pharmacologic control of blood pressure and vascular tone. Since the most common reaction to induction of anesthesia is hypotension with vasodilation,

patients with risk for profound hypotension including those with aortic stenosis, coronary artery disease, congestive heart failure, volume depletion, and pre-existing shock should have invasive arterial pressure measurement placed prior to induction of anesthesia and prophylactic hemodynamic management. Optimal hemodynamic control and stability can be achieved through the prophylactic addition of a vasoconstrictor such as intravenous infusion of phenylephrine prior to induction. Waiting for hypotension after induction, prior to administering multiple boluses of phenylephrine, followed by a delay to mix and start an infusion, causes prolongation of hypotension, and more hemodynamic instability. One can scramble around trying to treat the 95% of these patients who develop hypotension after induction or alternatively, start a prophylactic infusion of phenylephrine prior to induction, and discontinue it in the 5% who don't need it. Prophylactic initiation of phenylephrine infusions prior to induction in patients at risk of hypotension, reduces hemodynamic instability. The etiology of hypotension during anesthesia should be identified and corrected. Volume depletion is the most common etiology of hypotension, with vasodilation from lowered autonomic tone a close second. Vasoconstriction with phenylephrine can correct hypotension, reduce the need for excessive volume administration, and improve hemodynamics, all without stimulating the heart with a risk of myocardial ischemia.

The most common vasodilator used in anesthesia is an inhaled agent. When inhaled agents are inadequate to control blood pressure and vascular tone, or when a patient needs pharmacologic hemodynamic management for hypotension after anesthesia, there are multiple choices of vasodilators. The decision should begin with a diagnosis. Is

the hypertension from pain? A full bladder? Essential hypertension? Once pain has been adequately controlled and other causes corrected, any tachycardia should be corrected. If the heart rate is elevated, administration of beta blockade with intravenous metoprolol should be the next step. Once pain and heart rate are adequately controlled and hypertension is still an issue, then vasodilation with hydralazine, nitroprusside, nitroglycerine, clonidine, nicardipine, or clevidipine is the next step. The choice depends on timing and severity of hypertension. Intravenous hydralazine is excellent after neurosurgery or in patients with persistent hypertension that are otherwise hemodynamically stable. In patients after cardiac surgery or where hemodynamic instability is expected, a short acting intravenous vasodilator may be more appropriate. Nitroprusside is a nitric oxide donor and rapid arterial vasodilator which will increase cardiac output through afterload reduction. Nitroglycerine is a nitric oxide donor which requires metabolism to make NO. It has more of an effect on venous beds than nitroprusside. Nitroglycerine can make patients more volume sensitive as it vasodilates venous capacitance beds, reducing venous return and cardiac output. Nitroglycerine is NOT a selective vasodilator. Intravenous nitroglycerine administration vasodilates most vascular beds uniformly lowering systemic vascular resistance and blood pressure while maintaining coronary blood flow constant. Relative myocardial oxygen availability, as defined by the amount of oxygen utilized divided by the amount of oxygen available, is improved. The amount of oxygen available is constant while the oxygen demand is decreased. Intravenous nitroglycerine does not selectively increase coronary blood flow. Nitroglycerine does improve relative oxygen availability while maintaining coronary blood flow constant.

Optimal hemodynamic control of blood pressure requires rapid diagnosis of the etiology of the hemodyanmic problem, control of blood volume, heart rate, and vasoconstriction or vasodilation. Vasocontriction with phenylephrine boluses and infusions can provide optimal hemodynamic control in the critically ill or patients with multiple co-existing medical conditions such as coronary artery disease or aortic stenosis.

Inotropes:

Inotropes can be used in situations where cardiac output remains inadequate after optimizing vascular function (resistance and blood volume). Adequacy of cardiac output can be established through measurement using cardiac output monitoring or mixed venous saturation. Inotropic agents such as epinephrine, norepinephrine, dobutamine, milrinone, or amrinone should be selected based on the systemic vascular resistance, pulmonary vascular resistance, and heart rate needed to optimize vascular function and maximize ventricular efficiency. In situations where ventricular function is profoundly depressed and infusions of epinephrine and/or norepinephrine are inadequate, and where the heart rate and systemic vascular resistance are elevated, while cardiac output is inadequate, combinations of agents can achieve synergistic increases in cardiac output with fewer side effects. The combination of epinephrine or norepinephrine with a type-3 phosphodiesterase such as milrinone or amrinone, will provide synergistic increases in inotropic state and cardiac output. Epinephrine or norepinephrine stimulate beta receptors in the heart, increasing inotropic state but simultaneously vasoconstrict the vasculature, raising systemic vascular resistance and afterload. The addition of milrinone or amrinone to a beta agonist will 1) synergistically stimulate the heart to increase inotropic state by

prolonging the half life of cAMP by preventing its metabolism, 2) vasodilate peripherally lowering afterload, and 3) increase cardiac output. The combination of a catecholamine and a type-3 phosphodiesterase inhibitor causes synergistic increases in intropic state while balancing the effects on systemic vascular resistance and afterload. Phosphodiesterase inhibitors Types-1 through 4 work with cAMP dependent phosphodiesterases and Type-5 works with cGMP. Very careful adjustments of systemic vascular resistance are essential for optimal hemodyanamics. Placement of an intra-aortic balloon pump is frequently helpful in these situations to increase diastolic blood pressure and improve coronary blood flow.

Risks of Inotropes:

There are significant risks from inotropes which must be balanced against the need to support cardiac output. Catecholamines can be used as inotropic agents to increase cardiac output and improve hemodynamics,[46] but have significant risks including arrythmias,[46-48] myocardial ischemia,[49] infarction, hypokalemia,[50] and hyperglycemia.[51] Administration of catecholamines has been shown to decrease survival in patients with congestive heart failure,[52] when compared to vasodilators.[53] Rare trials show improved survival with dobutamine in congestive heart failure,[54] but most show decreased survival.[55,56] In contrast, beta blockaders, which are negative inotropes, improve long term cardiac function[57] and survival in congestive heart failure.[58,59] Even in patients with congestive heart failure after myocardial infarction, beta blockade improves survival.[60] Stimulation of the myocardium with catecholamines can be detrimental and increase morbidity and mortality.

The standard therapy for congestive heart failure includes vasodilation and afterload reduction because lowering the load on the heart improves cardiac output and efficiency while reducing oxygen consumption (Figure 7C Bottom Panel). The standard therapy during an acute myocardial infarction is to lower the load on the heart using beta blockers.[61-63] Increasing the load on the heart with catecholamines can be detrimental, increasing morbidity and mortality.[52] Blocking the end organ effect of catecholamines with beta blockers,[64-67] as well as lowering catecholamine production with the alpha-2 agonist clonidine,[68] has been shown to reduce perioperative mortality. Catecholamines should only be used to increase cardiac output when other measures, such as volume administration and afterload optimization have failed, and cardiac output is clearly inadequate.

Nitric Oxide:

The type-5 phosphodiesterase inhibitors (sildenafil, vardenafil) can be used to lower pulmonary vascular resistance. Their use in combination with nitrates must be done carefully, as there will be synergistic effects between the nitric oxide produced by nitrates (nitroglycerine or nitroprusside) and the type-5 phosphodiesterase inhibitors. Figure 9 details the biochemical effects of type-5 phosphodiesteases. Type-5 phosphodiesterase inhibitors will drop systemic blood pressures by 5 mmHg.[44] Type-5 phosphodiesterase inhibitors combined with nitrates will result in larger decreases in blood pressure unless blood volume is increased slightly.[44] Inhibition of nitric oxide effects can be achieved with methylene blue which may normalize blood pressure in the face of vasoplegic shock.[45]

Summary:

The present chapter has summarized the Control of Blood Pressure and Vascular Tone covering the physiology, autonomic nervous system function, vascular mechanics, ventricular mechanics, and pharmacology of commonly used vasoactive drugs. Hemodynamic problems are usually quite simple to solve if the root cause is rapidly identified. Vascular volume is the most common problem followed by systemic vascular resistance. *Hypotension and tachycardia are the result of volume depletion until proven otherwise.* Matching vascular impedance, both venous and arteriolar, to the heart provides optimal energy transfer and maximal cardiac output. Cardiogenic causes of low cardiac output such as diastolic dysfunction, systolic dysfunction, and myocardial ischemia need to be rapidly identified and corrected. External causes such as tamponade or tension pneumothorax should be viewed as essentially diastolic dysfunction, and must be rapidly corrected. Pulmonary hypertension raises right ventricular afterload and can lead to right ventricular failure and hemodynamic collapse. Anesthesia dramatically influences the autonomic, vascular, and ventricular function. A primary role of anesthesiology is correcting hemodynamic problems through appropriate pharmacologic and non pharmacologic control of blood pressure and vascular tone.

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FIGURE LEGENDS

Figure 1. Autonomic control of hemodynamics. The top panel shows the basics of the closed loop control system. Blood pressure measured by the baroreceptors is fed back to the NTS to achieved closed loop control and increased stability. The lower panel shows the complete control system with multiple inputs to the NTS as well as the two output systems (sympathetic and parasympathetic) and the multiple output variables in the cardiovascular system.

Figure 2. Interaction of left and right carotid sinus baroreceptor systems demonstrating inhibition of one carotid sinus baroreceptor reflex by high pressure in the contralateral system. Denervation or low contralateral pressure allows full reflex control by the ipsilateral reflex. Greene AS, Brunner MJ, Shoukas AA. Am J Physiol. 1986 Jan;250(1 Pt 2):H96-107

Figure 3. Effect of hemorrhage on blood pressure with and without inhibition of autonomic function. A 10% hemorrhage has little effect on blood pressure if autonomic function is intact. With inhibited autonomic function reduction in blood volume reduces blood pressure.

Figure 4. Ventricular pressure-volume relationship. Gray area is stroke work. Black area is potential energy. LVP: Left ventricular pressure. LVV: Left ventricular volume. SV: stroke volume.

Figure 5. Ventricular Pressure-Volume Relationship. LVP: Left ventricular pressure. LVV: Left ventricular volume. SV: stroke volume.

TOP: Top panel shows the pressure-volume relationship of an isovolumic contraction. No external work is done. The black area represents the potential energy of an isovolumic contraction with energy stored in the pressurized blood in the ventricle.

BOTTOM: Bottom panel shows the pressure-volume relationship of an ejecting beat. The black area is the potential energy of the pressurized blood at the end of systole. The gray area is the external work from the ejection. The sum of the gray and black area is the total energy of the contraction and is proportional to the total oxygen consumed to pump blood.

Figure 6. Ventricular Pressure-Volume Relationship with pharmacologic changes in afterload. LVP: Left ventricular pressure. LVV: Left ventricular volume. SV: stroke volume.

A: Top Panel: Baseline pressure-volume relationship for comparison. Black area is potential energy. Gray area is external work. Total of gray and black area is total energy consumed and is proportional to total oxygen consumed. Efficiency is gray area divided by sum of gray and black areas.

B: Middle Panel: Effect of increased afterload by vasoconstriction with phenylephrine. Notice the increase in total energy and total oxygen consumption with a reduction in stroke volume and cardiac output. Total energy (black area + gray area) is increased.

Total oxygen consumption is increased. Efficiency is reduced (gray area/(black + gray area)).

C: Bottom Panel: Effect of reduction in afterload by vasodilation with nitroprusside. Notice the decrease in total energy and total oxygen consumption with an increase in stroke volume and cardiac output. Efficiency is increased (gray area/(black + gray area)). Cardiac output is increased while reducing oxygen consumption and improving efficiency.

Figure 7. Optimization of cardiac function by impedance matching of vasculature to ventricle.

A: Top Panel: Schematic diagram of cardiovascular system with input (Z_{in}) and output (Z_{out}) impedance of heart as well as input (Z_{in}) and output (Z_{out}) impedance of vasculature. Optimal energy transfer and cardiac function occurs when output impedance (Z_{out}) is equal to the input impedance (Z_{in}). Output impedance of venous system should equal the diastolic input impedance of heart. Output impedance of heart during systole should equal input impedance of arterial vasculature.

B: Middle Panel: Ventricular Pressure-Volume Relationship with variation in elastance. Ventricular elastance (pressure/volume) changes with the cardiac cycle varying from end-diastole to end-systole and then back to end-diastole with each contraction.

C: Bottom Panel: Relationship between Ventricular End-Systolic Elastance (E_{ES}) and Arterial Elastance (E_{EA}). When arterial elastance E_{EA} equals ventricular systolic elastance E_{ES}, ventricular systolic output impedance equals arterial input impedance and there is optimal energy transfer and optimal cardiac output.

Figure 8. Relationships between Oxygen Consumption and Coronary Blood Flow when Heart Rate and Blood Pressure Vary.

A: Top Panel: Relationship between heart rate and oxygen consumption per beat and coronary blood flow. Plot demonstrates ischemic threshold with increasing heart rate secondary to reduction in diastolic time with reduction in coronary blood flow to left ventricle.

B: Bottom Panel: Relationship between blood pressure and coronary blood flow and oxygen consumption. Increases in blood pressure simultaneously increase coronary blood flow and oxygen consumption. There is no ischemic threshold with increases in blood pressure.

Figure 9: Biochemical mechanism of Type III (cAMP) and Type V (cGMP) phosphodiesterase inhibitors (PDE-I). For cGMP systems, receptor activation causes conversion of L-arginine into L-citrulline by nitric oxide synthetase with production of nitric oxide. Nitric oxide then causes conversion of GTP into cGMP. cGMP is metabolized into GMP by type V phospodiesterase. Type 1-4 phosphodiesterase work with ATP based systems converting cAMP into AMP. Phosphodiesterase inhibitor blocks action of phosphodiesterase, increasing levels of cAMP or cGMP, increasing effects of receptor activation. Examples of Type 1 PDE-I: caffeine, Type 2 PDE-I: theophyline, Type 3 PDE-I: amrinone and milrinone, Type 4 PDE-I unknown, Type 5 PDE-I: sildenafil, vardenafil.

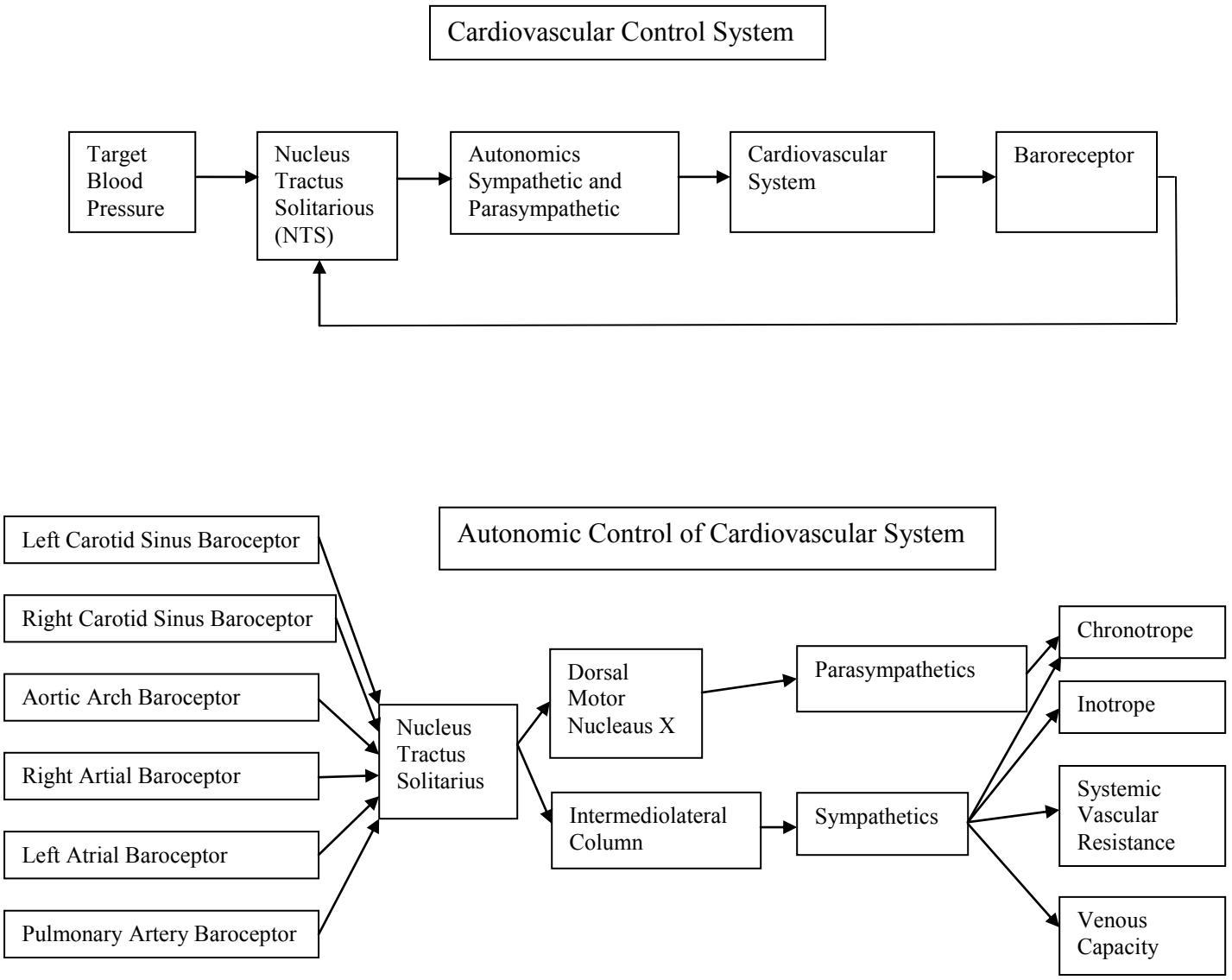

Cardiovascular Control System
Target Blood Pressure
Nucleus Tractus Solitarious (NTS)
Autonomics Sympathetic and Parasympathetic
Cardiovascular System
Baroreceptor
Autonomic Control of Cardiovascular System
Left Carotid Sinus Baroceptor
Right Carotid Sinus Baroceptor
Aortic Arch Baroceptor
Right Artial Baroceptor
Left Atrial Baroceptor
Pulmonary Artery Baroceptor
Nucleus Tractus Solitarius
Dorsal Motor Nucleaus X
Intermediolateral Column
Parasympathetics
Sympathetics
Chronotrope
Inotrope
Systemic Vascular Resistance
Venous Capacity

Figure 1

Baroreceptor Control of Arterial Pressure

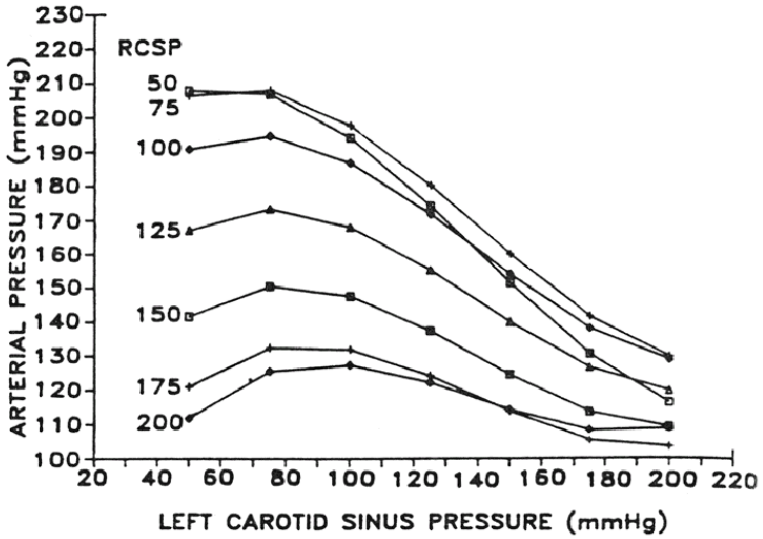


Figure 2

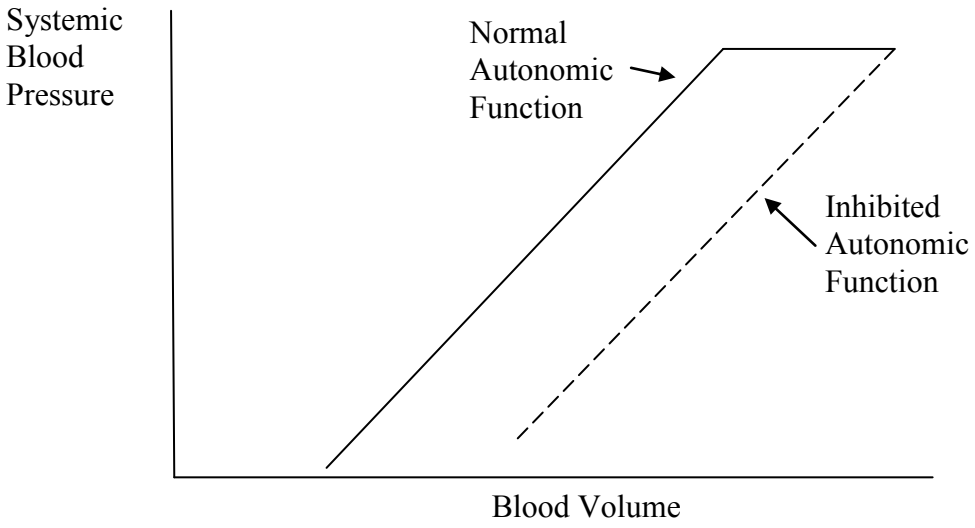

Systemic
Blood
Pressure
Normal
Autonomic
Function
Inhibited
Autonomic
Function
Blood Volume

Figure 3

Figure 4:

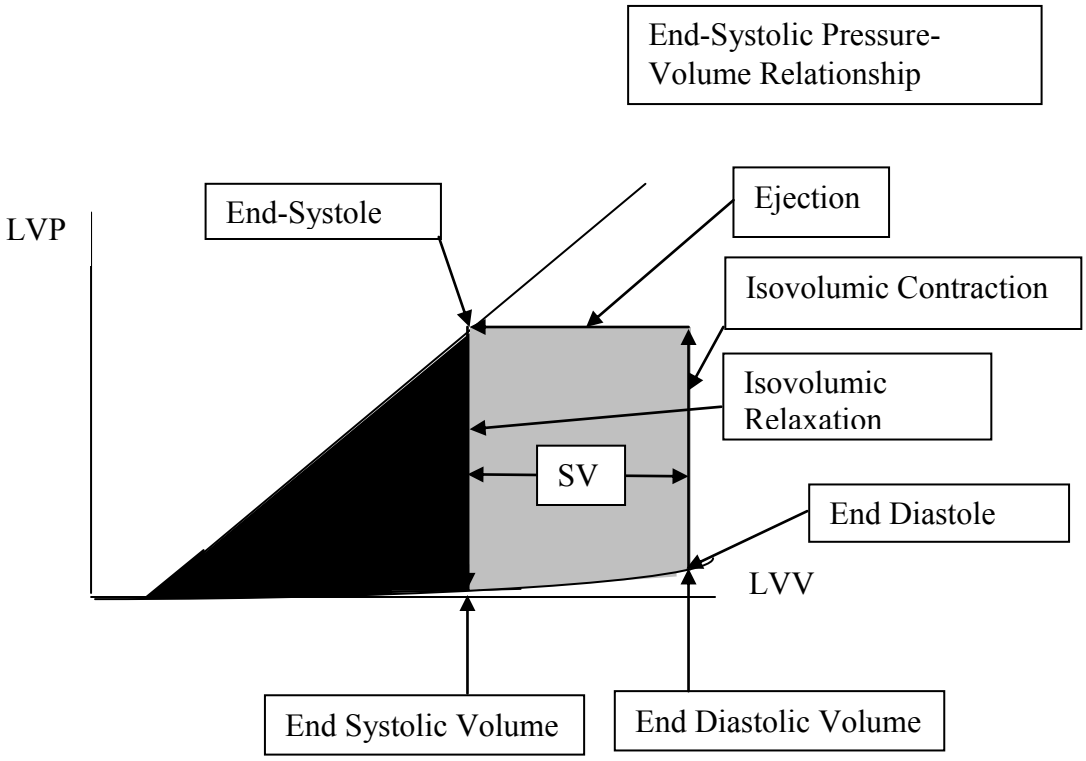

End-Systolic Pressure-Volume Relationship
LVP
End-Systole
Ejection
Isovolumic Contraction
Isovolumic Relaxation
SV
End Diastole
LVV
End Systolic Volume
End Diastolic Volume

Figure 5

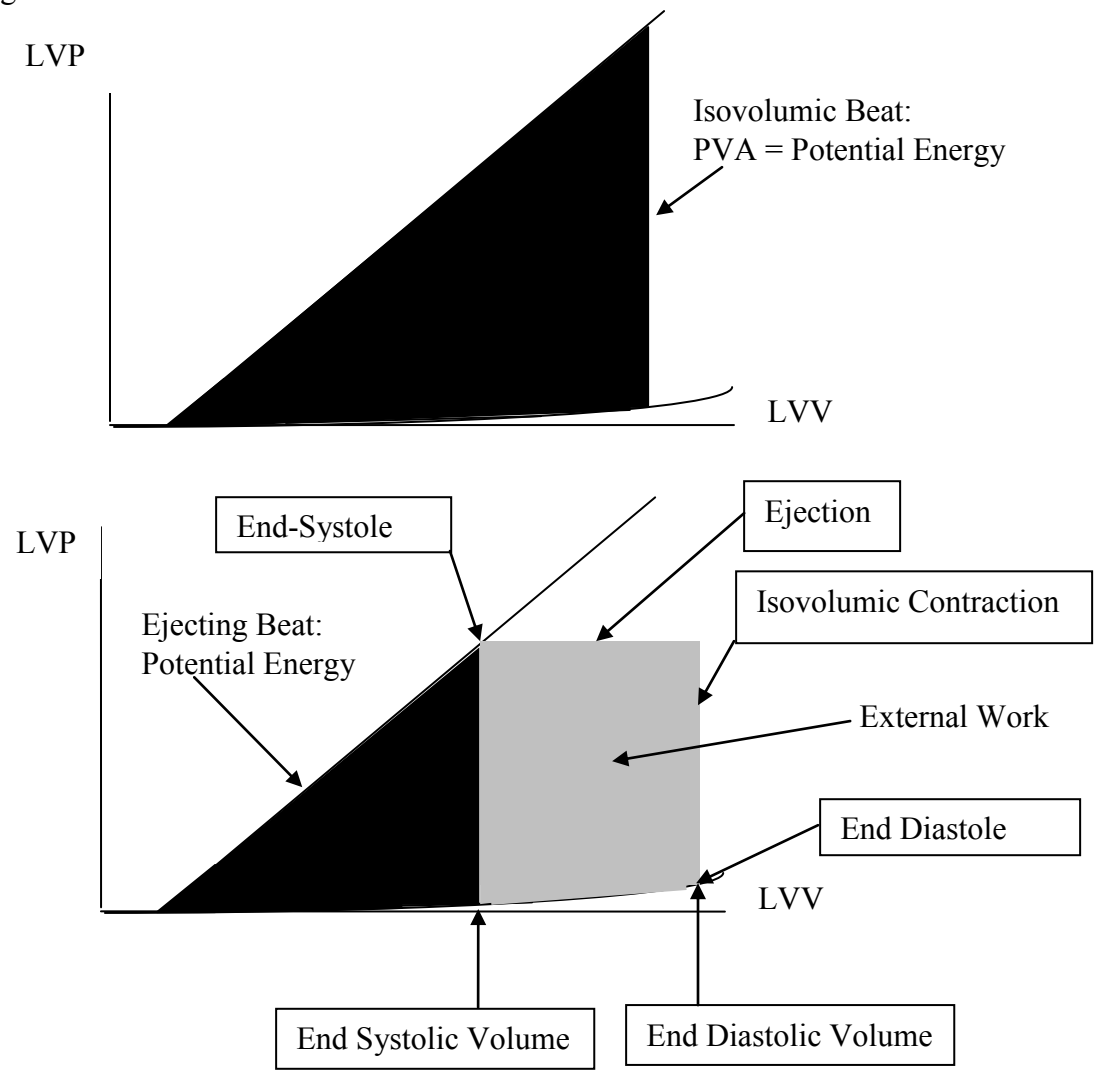

LVP
Isovolumic Beat:
PVA = Potential Energy
LVV
LVP
End-Systole
Ejection
Isovolumic Contraction
Ejecting Beat:
Potential Energy
External Work
End Diastole
LVV
End Systolic Volume
End Diastolic Volume

Figure 6

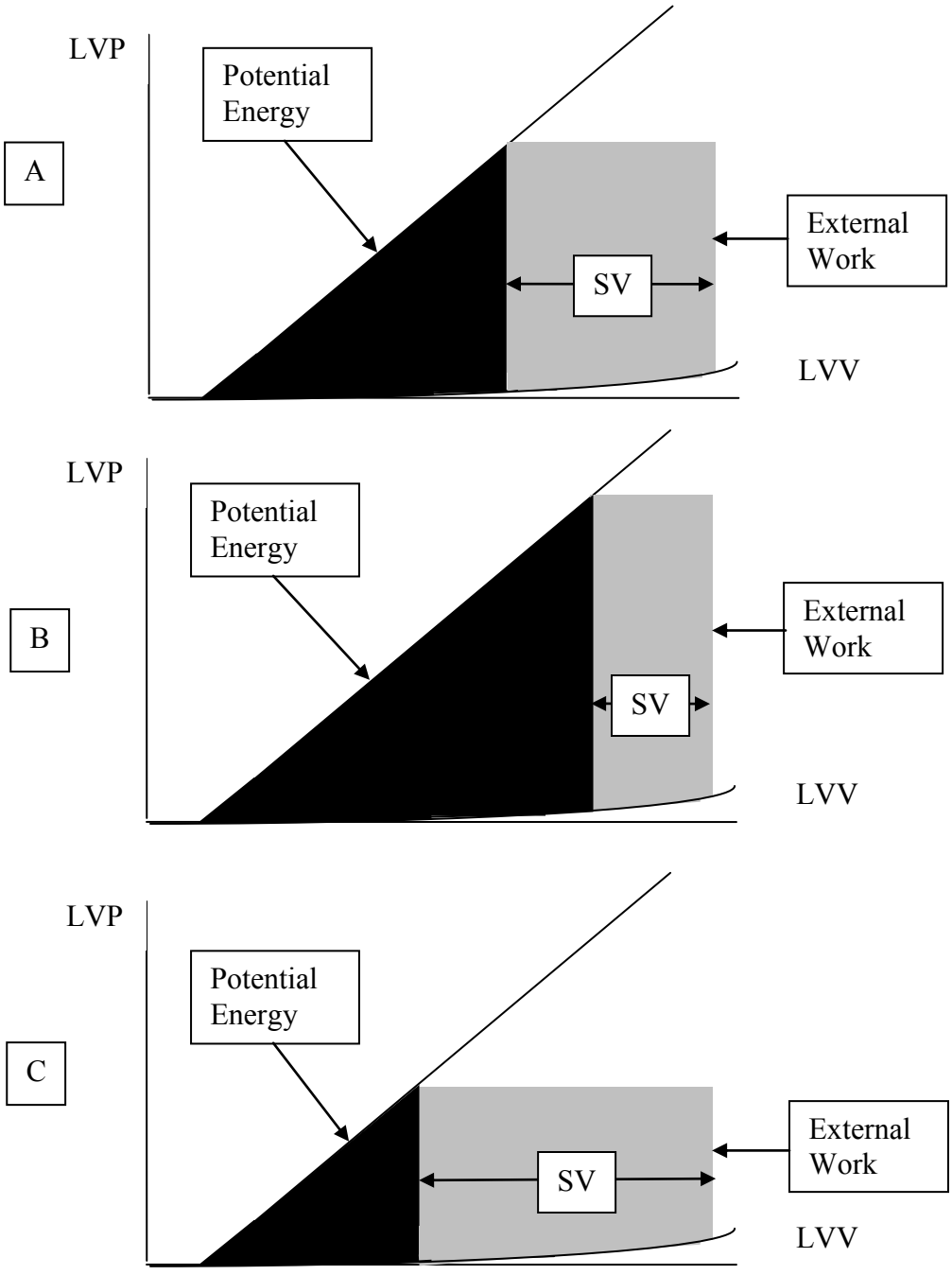

LVP
Potential Energy
A
External Work
SV
LVV
LVP
Potential Energy
B
External Work
SV
LVV
LVP
Potential Energy
C
External Work
SV
LVV

Figure 7.

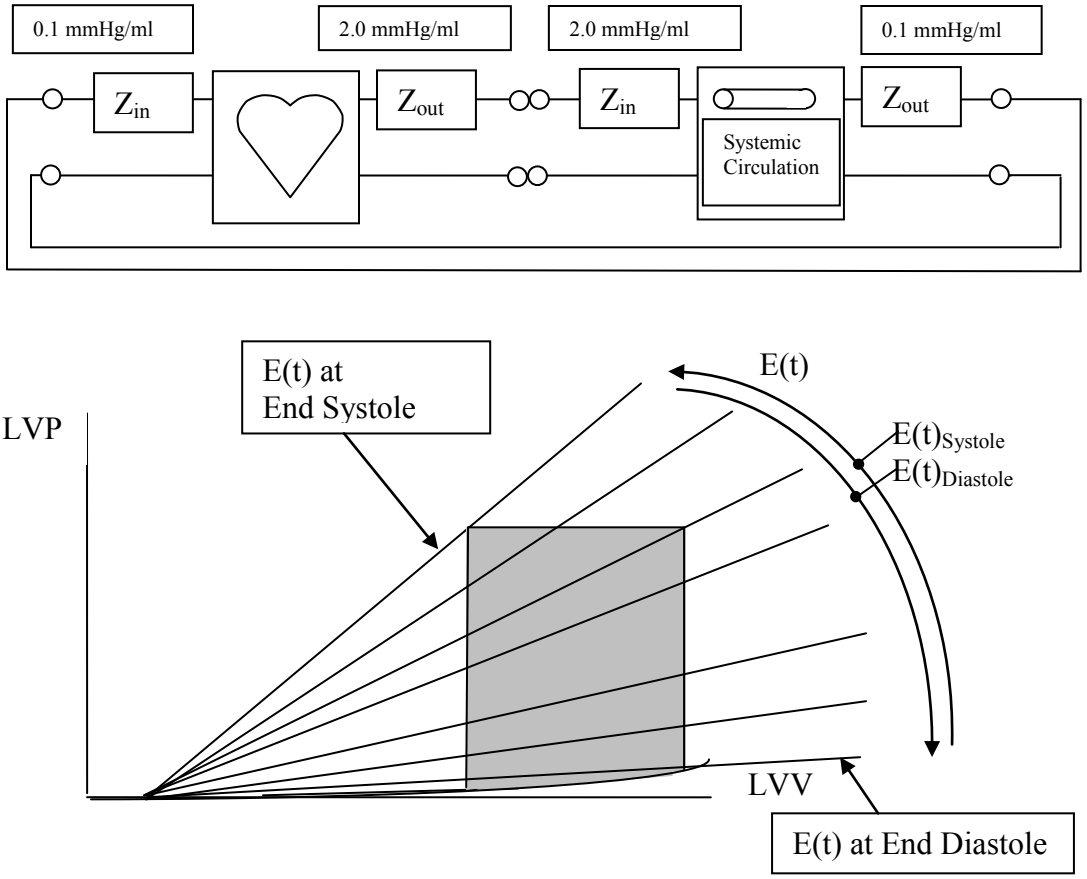
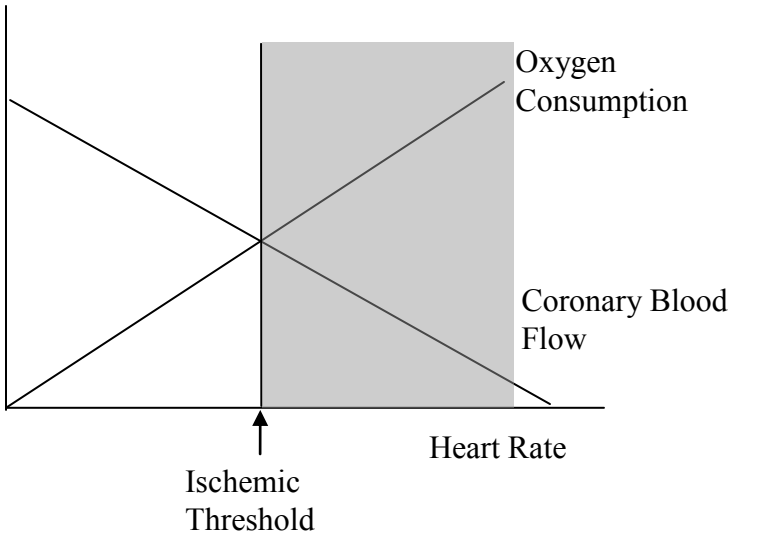
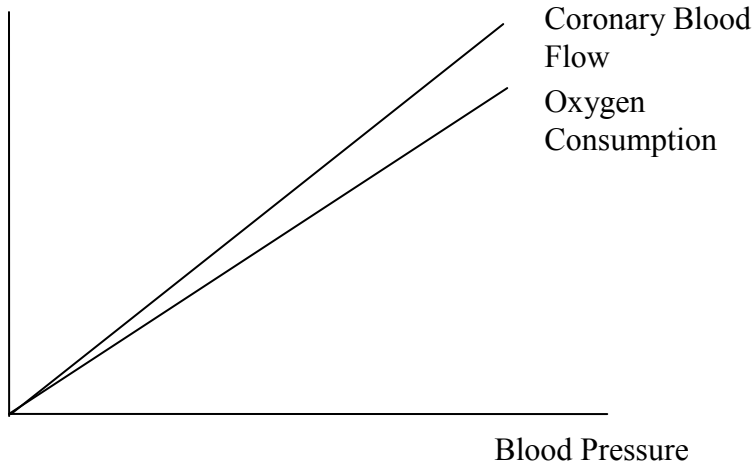

0.1 mmHg/ml
2.0 mmHg/ml
2.0 mmHg/ml
0.1 mmHg/ml
Z_{in}
Z_{out}
Z_{in}
Z_{out}
Systemic Circulation
E(t) at End Systole
E(t)
$E(t)_{Systole}$
$E(t)_{Diastole}$
LVP
LVV
E(t) at End Diastole
LVP
E_{EA} (Arterial)
E_{ES} (Ventricular)
LVV

Figure 8


Oxygen
Consumption
Coronary Blood
Flow
Heart Rate
Ischemic
Threshold


Coronary Blood
Flow
Oxygen
Consumption
Blood Pressure

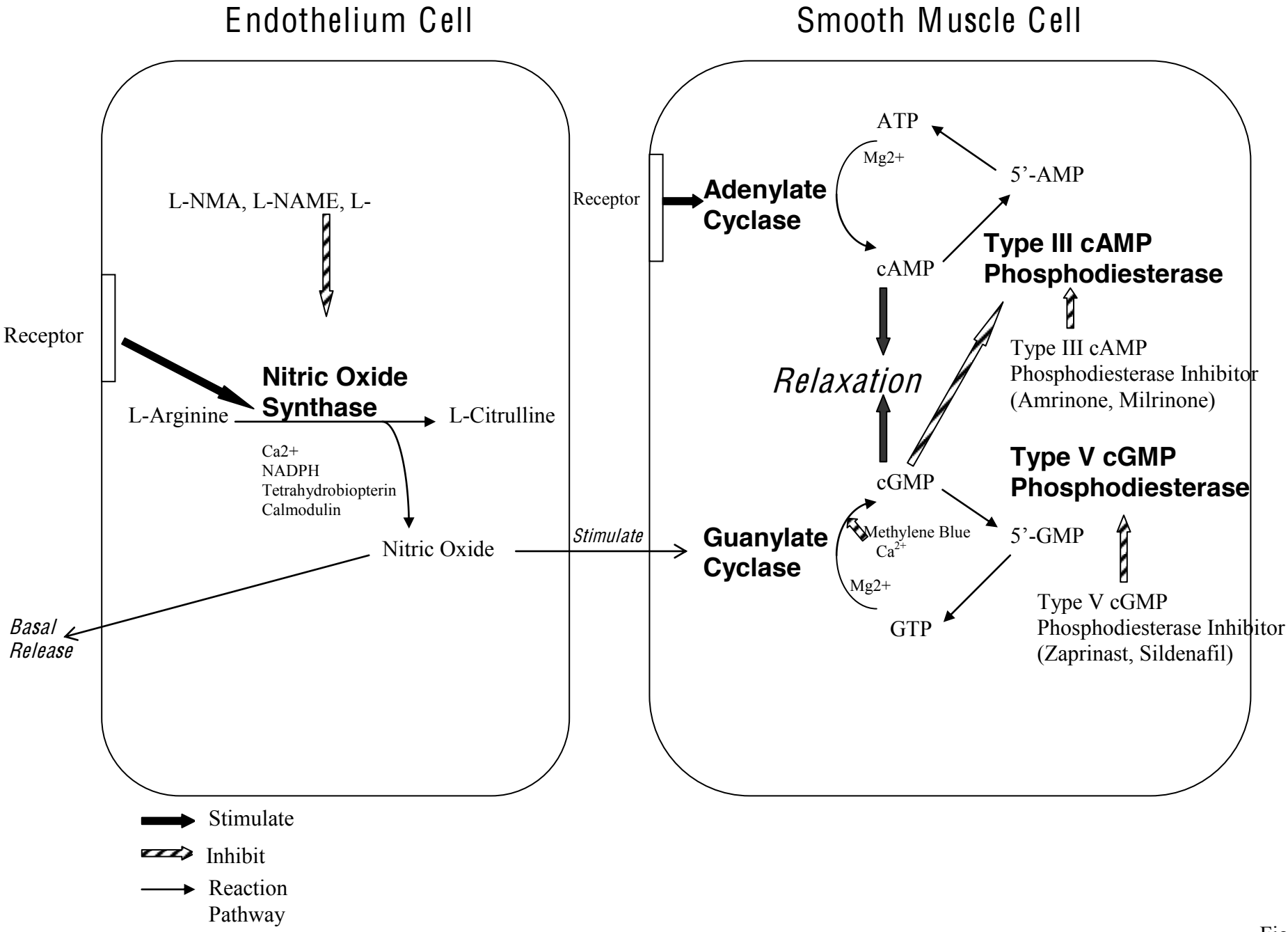

Endothelium Cell
Smooth Muscle Cell
L-NMA, L-NAME, L-
Receptor
Nitric Oxide Synthase
L-Arginine
L-Citrulline
Ca2+
NADPH
Tetrahydrobiopterin
Calmodulin
Nitric Oxide
Basal Release
Stimulate
Receptor
Adenylate Cyclase
ATP
Mg2+
5'-AMP
cAMP
Type III cAMP Phosphodiesterase
Type III cAMP Phosphodiesterase Inhibitor (Amrinone, Milrinone)
Relaxation
Type V cGMP Phosphodiesterase
cGMP
Guanylate Cyclase
Methylene Blue
Ca2+
Mg2+
5'-GMP
GTP
Type V cGMP Phosphodiesterase Inhibitor (Zaprinast, Sildenafil)
Stimulate
Inhibit
Reaction Pathway

Figure 9

Table 1: Target or Mechanism of Action and Physiologic Effect of Many Cardiovascular Therapeutic Agents.

	Target or mechanism of action						Physiologic Effect				
Drug	Alpha	Beta	Dopa	PDE-I	Nitric Oxide	Vasopressin	HR	MAP	SVR	Inotropic	CO
Metoprolol		-					↓	↓	–	↓	↓
Isoproterenol		+					↑	±	↓	↑	↑
Dobutamine		+					↑	±	↓	↑	↑
Dopamine	+	+	+				↑	↑	↑	↑	↑
Epinephrine	+	+					↑	↑	↑	↑	↑
Norepinephrine	++	+					↑	↑	↑↑	↑	↑
Phenylephrine	+						↓ or none	↑	↑	none	↓
Amrinone				+ Type 3			±	↓	↓	↑	↑
Milrinone				+ Type 3			±	↓	↓	↑	↑
Sildenafil				+ Type 5			±	↓	↓	↑	↑
Nitroglycerine					+		↑ or none	↓	↓	None	↓
Nitroprusside					+		↑ or none	↓	↓	None	↑
Nitric Oxide					+		–	–	PVR ↓	-	–
Methylene Blue					–		–	↑	↑	-	–
Vasopressin						+	↓ or none	↑	↑	None	↓

Table 1:
Alpha: Alpha Receptor
Beta: Beta Receptor
Dopa: Dopaminergic Receptor
PDE-I: Phosphodiesterase inhibitor
HR: Heart Rate
MAP: Mean Arterial Pressure
SVR: Systemic Vascular Resistance
CO: Cardiac Output