CORONARY ARTERY PATHOPHYSIOLOGY

Dr. LeRoy E. Rabbani and Dr. Robert H. Heissenbuttel

Learning Objectives:

1. Understand the major determinants of myocardial oxygen demand and supply.

2. Understand the compensatory mechanism of autoregulation in the maintenance of coronary artery blood flow.

3. Understand the vital importance of the healthy endothelium in vascular biology and of endothelial dysfunction in pathologic states.

4. Understand the vital roles of coronary artery collateral circulation and coronary artery remodeling in the pathogenesis of coronary artery disease.

5. Fully understand the underlying pathophysiology and treatment of the acute coronary syndromes.

6. Understand the role of inflammation in the pathogenesis of coronary artery disease and the acute coronary syndromes.

I. Coronary Anatomy

There are two coronary arteries, right and left, arising respectively from the right anterior and left anterior aortic sinus of Valsalva. The ostia are situated slightly above the reflections of the semilunar valves, the right coronary artery being 35° to the right and the left coronary artery 65° to the left of the anteroposterior axis of the body.

The left coronary artery courses anteriorly and to the left in the atrioventricular groove, between the pulmonary artery and the left atrial appendage, and bifurcates into its two major branches, the anterior descending and the circumflex. These branches are quite constant in all mammalian species. In human beings, the bifurcation occurs most commonly 1 to 1.5 cm from the ostium.

The left anterior descending (LAD) follows the anterior interventricular sulcus towards the apex and is of variable length, terminating prior to, at, or beyond the apex. There are from two to seven ventricular branches (diagonal branches) which course over the lateral wall of the surface of the left ventricle. Potential anastomoses exist between these ventricular branches and epicardial branches of both the right and circumflex coronary arteries. Septal branches of the left anterior descending coronary artery penetrate deeply from the underside of the vessel into the interventricular septum.

The left circumflex coronary artery follows the atrioventricular groove to the left, coursing under the left atrial appendage and terminating at a variable distance from the posterior interventricular groove. An average of three ventricular branches (marginal branches) and three atrial branches arise from the circumflex coronary artery. Posteriorly potential connections exist between the circumflex and the right coronary arteries, either through the posterior descending branch, which runs in the posterior longitudinal sulcus, through the lateral ventricular branches, or through the atrial branches.

The right coronary artery passes behind the pulmonary artery and follows the atrioventricular groove to the right margin of the heart. In human beings, approximately 80% of the time, the right coronary artery courses posteriorly around the heart and supplies the posterior descending branch. When this occurs, the right coronary artery is described as "dominant."

The arterial supply to the conducting system requires special comment because of its functional importance. Sixty to seventy percent of the time the major supply to the sinoatrial node (SA node artery) arises from the right coronary artery. The supply to the atrioventricular node (A-V node) is via the dominant coronary vessel, i.e., the right coronary artery (80% in human beings). In 10% of human subjects the A-V nodal artery arises from the circumflex, and in another 10% the A-V nodal artery arises from both the right and left systems.

The interventricular septum receives its blood supply from the penetrating branches of both the left anterior descending and the posterior descending coronary arteries. The septal branches of the LAD supply the anterior two-thirds to three-fourths of the septum. The posterior branches are shorter. The septal arteries provide a rich source of potential intramyocardial collateral flow between the LAD and the distal right coronary artery through the posterior descending artery.

There are twice as many venous as arterial channels in the heart, their density in the left ventricle greatly exceeding that in the right. The superficial left ventricular veins parallel the epicardial coronary arteries and course toward the base of the heart to enter the great cardiac vein anteriorly and its continuation in the left atrioventricular groove, the coronary sinus, posteriorly.

The coronary sinus empties into the right atrium in the posterior-inferior interatrial septum located between the medial end of the inferior vena cava and A-V ring. The left coronary artery accounts for all but 5 to 10% of coronary sinus outflow. Eighty to eighty-five percent of left coronary inflow drains into the coronary sinus. The veins from the right ventricle are smaller and empty into sinusoids and from there directly into the left ventricle. These are referred to a thebesian veins.

II. Determinants of Myocardial O_2 Consumption

A. Determinants of Myocardial O_2 Demand

1. Tension (stress)
2. Contractility
3. Heart rate

1. Tension

By the Law of Laplace

T = Pressure x Radius

Pressure is intraventricular pressure and radius is the radius of the ventricular chamber. (More properly, we should deal with stress, which is force or tension development per unit of cross sectional wall area. Stress is thus inversely related to wall thickness.)

$$\text{Wall Tension} \propto \frac{P \bullet r}{h}$$

P = LV Systolic Pressure
r = LV Radius
h = Wall Thickness

O_2 consumption is linearly related to tension development if the other determinants of O_2 demand are held constant.

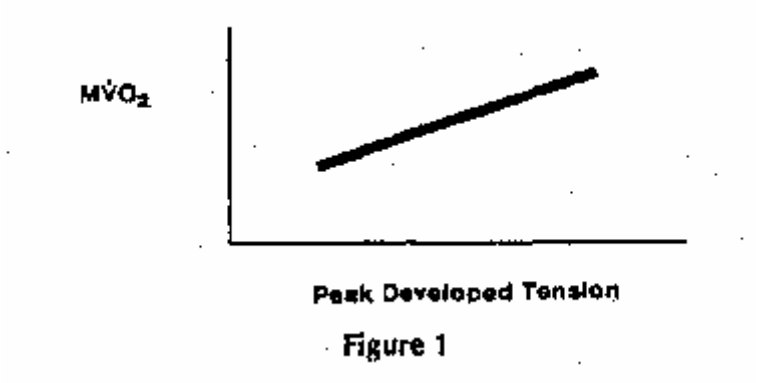
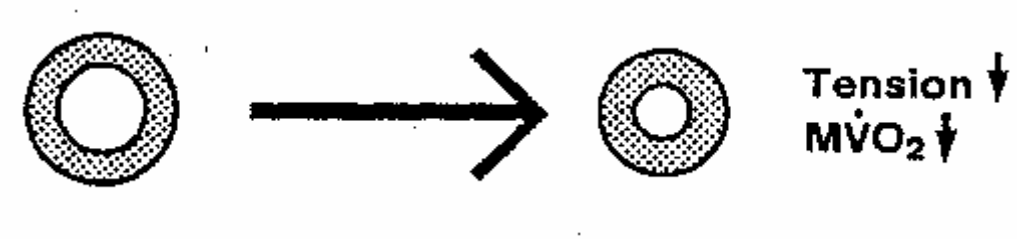


Figure 1

Increasing the radius of the heart increases the tension within the myocardial wall. Thus, if one is confronted with the situation of a large failing left ventricle which has become dilated in order to achieve a given level of stroke work (Frank-Starling Law), then administering an agent such as digitalis or one of the catecholamines which decreases the size of the heart will result in a decrease in wall tension on the basis of the La Place principle (Figure 2a). There will be a concomitant decrease in myocardial oxygen consumption (Figure 2a).

Thus, both ventricular pressure and size are important determinants of oxygen demand.

Figure 2a: Dilated Heart

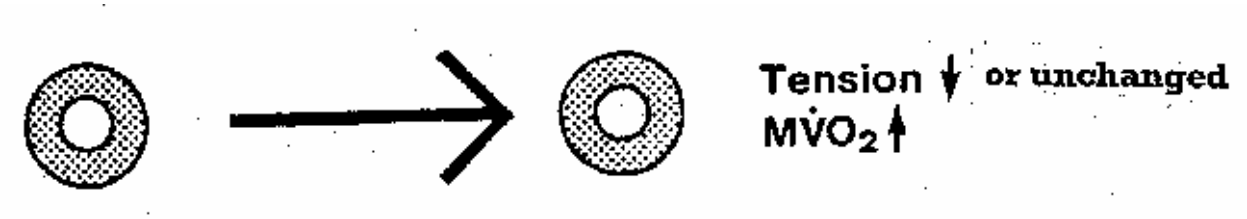


2. Contractility

When a positive inotropic agent is administered to a heart which is initially small, there is usually little to no change in ventricular size and little change or an actual decrease in the tension (Figure 2b). In this situation, a substantial increase in myocardial oxygen consumption occurs frequently (Figure 2b). Under these circumstances, the positive inotropic agent increases the velocity of ventricular contraction (which is directly related to myocardial oxygen consumption), and the concomitant small decreases in ventricular size and in tension are not sufficient to counterbalance the increase in myocardial oxygen consumption associated with the increase in velocity of contraction.

The effect of increasing contractility on chamber size and oxygen consumption in the normal sized heart is shown schematically in **Figure 2b.**

Figure 2b: Normal Sized Heart



Indeed, it is possible to have a substantial increase in myocardial oxygen consumption (up to 100% increase) associated with the increase in velocity of contraction produced by positive inotropic interventions in the face of considerable decreases in the tension, as shown in **Figure 3**.

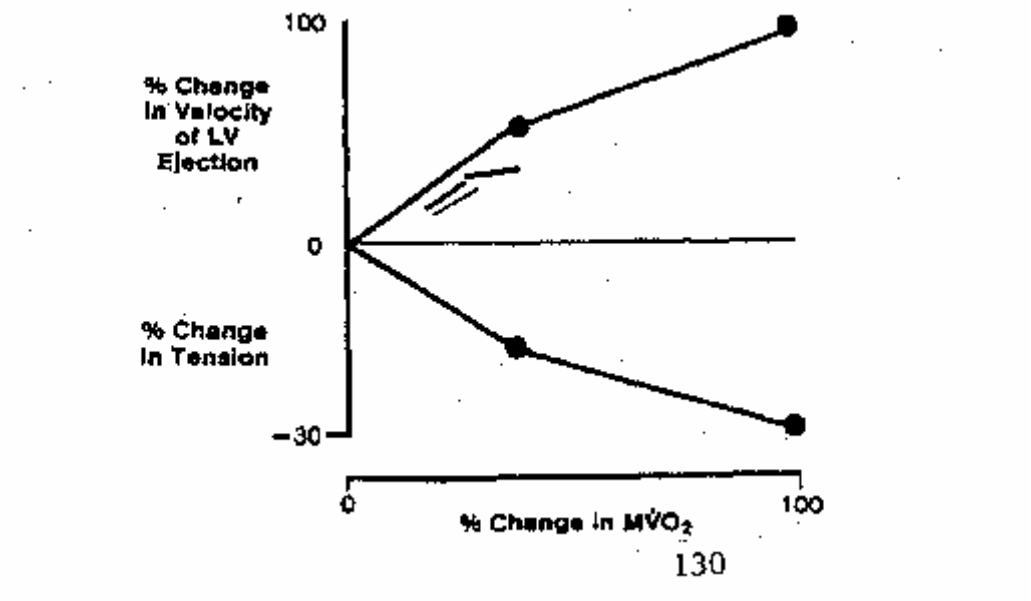


Figure 3

In these experiments, the positive inotropic interventions of norepinephrine (NE), calcium (CA), and an experimental technique known as paired stimulation (PS) were applied either individually or in combination. As can be seen along the horizontal axis at the bottom, the application of these techniques increased myocardial oxygen consumption substantially. These increases in myocardial oxygen consumption were associated with increases in the velocity of myocardial contraction (reflected in the left ventricular ejection velocity shown along the vertical axis of the top panel). The increases in oxygen consumption associated with the increments in velocity occurred despite concomitant deceases in tension, shown in the bottom panel. Thus, the influence of the increase in velocity of contraction outweighed the influence of the decrease in tension to produce a net substantial increase in myocardial oxygen consumption. This does not necessarily mean that velocity of contraction is a more important determinant of myocardial oxygen consumption than wall tension, since the net effect on oxygen consumption will depend on many circumstances which include the hemodynamic status of the heart before a given intervention is instituted.

The relationship between developed tension and contractility in the determination of MVO_2 is shown below.

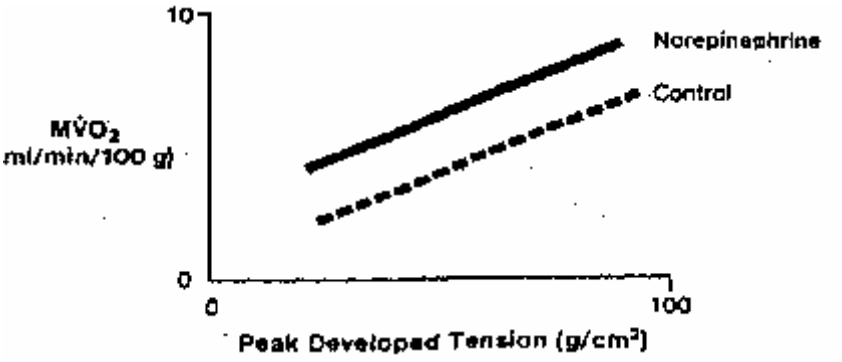
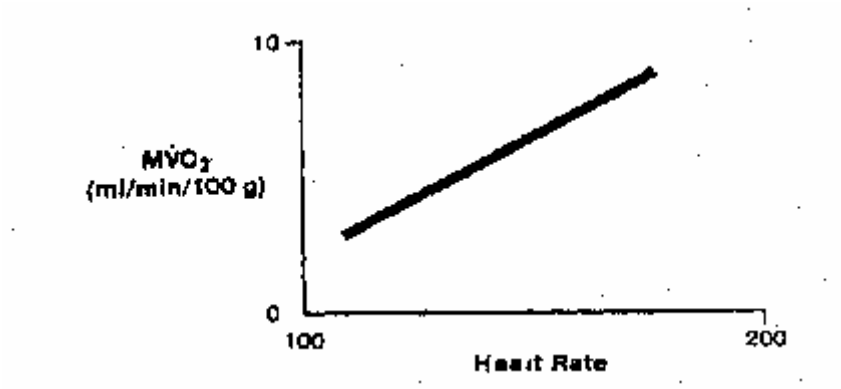


Figure 4

3. Heart Rate

The third major determinant of MVO_2 is heart rate. This is illustrated schematically in **Figure 5** below.



The increased heart rate seen with tachycardia not only increases myocardial oxygen consumption, it decreases coronary artery blood flow by decreasing the amount of time in the cardiac cycle spent in diastole during which coronary arterial blood flow is maximal. Clinically, particularly in situations where it is not feasible to measure myocardial oxygen consumption directly in patients, the product of heart rate multiplied by the peak systolic pressure has been used as a rough estimate of myocardial oxygen consumption. As we have seen, however the use of this index clinically does ignore ventricular size (reflected in left ventricular end-diastolic pressure) and velocity of contraction -- both of which are major correlates of myocardial oxygen consumption.

VARIATIONS IN WALL TENSION

↑ LV filling (MR, AI) ↑r and ↑ wall tension
↓ LV filling (nitrates) ↓r and ↓ wall tension
↑ LV systolic pressure (AS, HTN) ↑ wall tension
↓ LV systolic pressure (vasodilators) ↓ wall tension
↑ LVH (AS) ↓ wall tension
↑ Heart rate (tachycardia) ↑ wall tension

↓ Heart rate (β-blockers) ↓ wall tension
↑ Contractility (digoxin, catecholamines) ↓ wall tension or leaves wall tension unchanged in the normal sized heart but ↓ wall tension in the dilated heart
↓ Contractility (β-blockers) ↓ wall tension

B. DETERMINANTS OF O_2 SUPPLY

The three major determinants of myocardial oxygen supply are:

1. Diastolic Perfusion Pressure
2. Coronary Vascular Resistance
3. Oxygen Carrying Capacity

The oxygen carrying capacity of the blood is related to the hemoglobin content as well as systemic oxygenation. Therefore, in the absence of either anemia or pulmonary disease, the oxygen carrying capacity is fairly constant. As a result, myocardial oxygen supply is mainly determined by the diastolic perfusion pressure (maximal coronary artery blood flow occurs during diastole) and the coronary vascular resistance.

As noted above, diastolic perfusion pressure is of critical importance to the myocardial oxygen supply. Maximal coronary arterial blood flow occurs during diastole. During systole, the contracting myocardium compresses the coronary arteries. Moreover, during systole, there is a Venturi effect caused by a localized diminution in pressure along the sides of the proximal aorta owing to rapid blood flow through the narrow aortic outflow tract. Thus, the coronary arterial ostial systolic pressure is lower than the aortic systolic pressure, thereby resulting in decreased systolic perfusion pressure into the coronary arteries. In contrast, during diastole, the relaxed myocardium does not compress the coronary arteries, and the aortic valve is closed, obviating the Venturi effect.

The heart is nearly a purely aerobic organ. Therefore, its metabolism depends on continuous oxygen supply. Theoretically, oxygen supply could be adjusted to meet demand, either by changing blood flow or by changing oxygen extraction. However, even in basal conditions the heart extracts nearly all available oxygen from the blood. For the body as a whole, approximately 25% of the oxygen in the arterial blood normally is removed during passage from the arterial to the venous circulation. The heart extracts approximately 70% of the oxygen in every milliliter of blood, leaving coronary sinus blood about 30% saturated at a pO_2 of 18 to 20 mm Hg.

This near-complete extraction of oxygen is affected very little by changes in oxygen demand. Therefore, changes in oxygen supply to match changes in oxygen demand can be accomplished only by changing myocardial blood flow.

Before we discuss the effects of disease on myocardial blood flow, we will discuss the determinants of blood flow in the normal heart. Myocardial flow is determined by driving pressure and coronary vascular resistance.

$$Q \alpha \frac{P}{R}$$

Q = Coronary Artery Blood Flow

P = Perfusion Pressure

R = Coronary Vascular Resistance

The perfusion pressure (P) is usually held constant by baroreceptor regulation. Therefore, coronary artery blood flow (Q) is primarily the result of coronary vascular resistance (R).

The regulators of coronary ventricular resistance are:

1. Metabolism
2. Autoregulation
3. The Endothelium
4. Mechanical factors (extra vascular compression)
5. Neural factors

In the normal heart, coronary blood flow is closely linked to oxygen demand. This is accomplished by means of metabolic mediators. Although the other regulators listed above (2-5) influence blood flow as described below, changes in metabolism (1) are preeminent and control myocardial flow.

1. Metabolism

The metabolic mediator or mediators which provide the link between myocardial metabolism and blood flow have not been positively identified. Current evidence suggests adenosine as the most likely candidate. Adenosine is an extremely potent vasodilator. It is formed at myocardial cell surfaces from the dephosphorylating action of 5' nucleotidase on AMP, which in turn is derived from the breakdown of ATP and ADP. Adenosine can diffuse from the myocardial cell into the interstitial space and effect vasodilation. It subsequently can be phosphorylated by the enzyme adenosine kinase to form AMP, or it can be deaminated by adenosine deaminase to form its metabolite, inosine. Other potential mediators of the metabolic link between oxygen demand and blood supply include CO_2, O_2 (a vasoconstrictor), K^+, osmolarity, bradykinin, prostaglandins (particularly prostacyclin), lactate and hydrogen ions.

2. Autoregulation

Under experimentally controlled conditions in which myocardial activity and, thus, metabolic

requirements of the heart are maintained constant, coronary flow remains nearly constant despite large changes in coronary arterial perfusion pressure. This is termed autoregulation. Autoregulation is rarely observed in the normal situation because changes in coronary arterial perfusion pressure are produced by changes in aortic pressure which result in changes in oxygen demand, leading to changes in metabolic determinants of flow and, thus, changes in flow. Autoregulation may be important distal to a coronary arterial obstruction. Since perfusion pressure distal to an obstruction is decreased, autoregulation would tend to compensate, causing a decrease in resistance and a maintenance of blood flow. The mechanisms which determine autoregulation are not well understood.

Figure 6 below can be seen the effects of autoregulation, changes in metabolic need, and maximal vasodilation with a powerful vasodilator, and the relationship between coronary perfusion pressure and coronary blood flow.

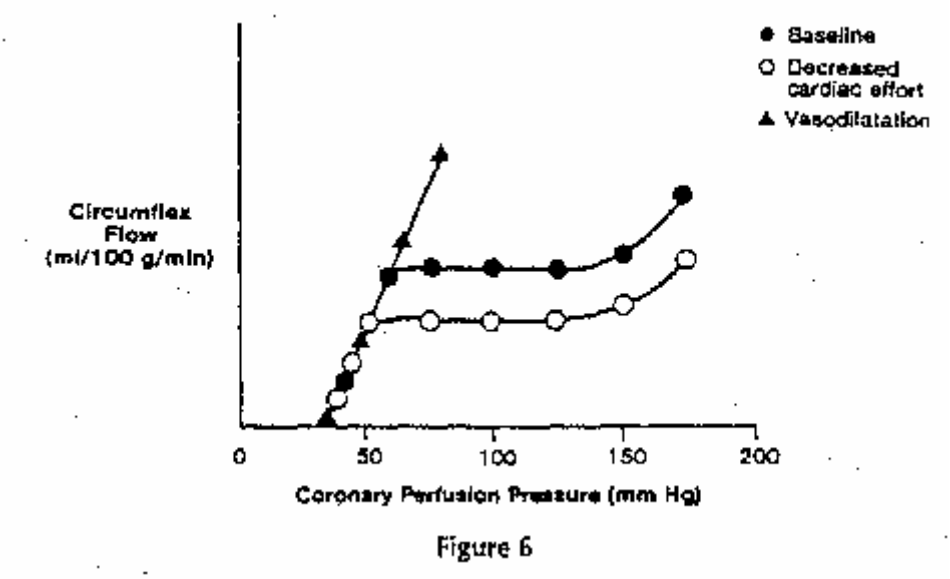


Figure 6

In the perfusion pressure range 50-150, change in metabolic demand lowers or raises the whole flow curve to a different level. Autoregulation keeps flow at that level over the range of perfusion pressure. Below 50 mm Hg or above 150 mm Hg in this experiment, these compensatory mechanisms become incomplete.

3. The Endothelium

The coronary endothelium plays an important role in coronary resistance. In a paper published in *Nature* in 1980, Furchgott and Zawadzki demonstrated that the relaxation of isolated arteries in response to acetylcholine depends on the presence of the endothelial cells in the preparation. An intact endothelium is required for acetylcholine-induced vasodilation. If the endothelium is removed, acetylcholine causes paradoxical vasoconstriction. Endothelial cells release a labile, diffusible substance with a very short half-life of a few seconds, initially called endothelium derived relaxing factor (EDRF), which relaxes vascular smooth muscle cells by

stimulating guanylate cyclase, resulting in increased cyclic GMP. EDRF release is stimulated by acetylcholine, ATP, ADP, bradykinin, histamine, thrombin, serotonin, substance P, and by increased vascular shear stress. EDRF release is apparently flow dependent and related to increased shear stress on the endothelial surface.

In animals, acute damage to coronary endothelium enhances the vasoconstrictor response. Experimental atherosclerosis in monkeys brought about by cholesterol feeding reduces the vasodilator response to drugs. Regression of atherosclerosis by lowering cholesterol restores the endothelial cell response. In man, atherosclerosis diminishes the normal vasodilator response to coronary acetylcholine infusion or converts it to vasoconstriction.

Indeed, while intracoronary nitroglycerin always results in coronary artery vasodilation, intracoronary acetylcholine results in vasodilation of normal coronary arteries but paradoxical vasoconstriction of atherosclerotic coronary arteries. Endothelium-dependent relaxation is diminished by atherosclerosis, hypercholesterolemia, diabetes, hypertension, cigarette smoking, estrogen deficiency, and advanced age. Treatment with cholesterol-lowering agents (HMG-CoA reductase inhibitors, cholestyramine) as well as the antioxidant probucol for 6-12 months improves the response to acetylcholine in human coronary arteries.

In addition to producing the vasodilator and anti-platelet aggregation agent EDRF, the endothelium also produces prostacyclin, a potent vasodilator and anti-platelet aggregation agent in its own right. Endothelial cells release prostacyclin in response to hypoxia and shear stress. Prostacyclin increases cAMP in vascular smooth muscle cells and platelets. EDRF and prostacyclin act synergistically to effect coronary arterial vasodilation and inhibit platelet aggregation. However, damaged or dysfunctional endothelium and atherosclerotic endothelium have impaired release of both prostacyclin and EDRF. High density lipoprotein (HDL), which has several anti-atherogenic actions, stimulates prostacyclin release from the endothelium and stabilizes it in the circulation.

It should be noted that only a few vasodilators act independently of the endothelium and act directly on vascular smooth muscle. These include prostacyclin, adenosine, and the nitrovasodilators (nitroglycerin and nitroprusside).

More recent studies have shown that at least one substance, the nitric oxide free radical (NO), has the same activity as EDRF, and it is the current view that nitric oxide is EDRF. Nitric oxide is continuously produced in endothelial cells by the enzyme nitric oxide synthase (NOS) from its precursor, L-arginine. Oxidation of the guanidine-nitrogen terminal of L-arginine results in NO formation. The NOS exists in various isoforms in endothelial cells, macrophages, platelets, vascular smooth muscle cells, nerves, and the brain. In endothelial cells, NOS is constitutively activated, but it can also be upregulated by shear stress and estrogens. An inducible form of NOS is present in vascular smooth muscle cells and macrophages, and it can be activated by cytokines such as endotoxin, interleukin-1β, and tumor necrosis factor. As shown for EDRF, nitric oxide acts on guanylate cyclase of vascular smooth muscle cells to stimulate cyclic GMP and produce vasodilation. Increased cGMP mediates vasodilation through inhibition of calcium release from the endoplasmic reticulum and other intracellular storage sites.

Vascular endothelial cells not only produce EDRF, or nitric oxide, causing vasodilatation, but also produce endothelin-1 (ET-1), a potent 21 amino acid peptide vasoconstrictor. Thus, the endothelial cell produces vasodilating and vasoconstricting substances which play a role in controlling coronary resistance. Pathologic states, such as coronary atherosclerosis, diminish or abolish vasodilator effects of EDRF. ET-1 may participate in vasoconstriction at sites of thrombi on ulcerated plaques. It may play a role in hypertension and is a potent smooth muscle cell (SMC) mitogen similar to platelet-derived growth factor (PDGF). Unlike EDRF, ET-1's actions last minutes to hours. Release of ET-1 is stimulated by thrombin, transforming growth factor β, interleukin-1, epinephrine, angiotensin II, arginine vasopressin, calcium ionophore, and phorbol ester. Endothelin attenuates the induction of inducible NOS. There are two distinct endothelin receptors - the ET_A- and ET_B- receptors, both of which are G-protein-coupled and linked to phospholipase C and protein kinase C. In addition to the vasoconstrictor response to endothelin, the endothelium is also susceptible to vasoconstriction from cyclooxygenase pathway products such as thromboxane A_2 and prostaglandin H_2 which are stimulated by arachidonic acid, acetylcholine, histamine, and serotonin as well as superoxide anions which inactivate NO to form the cytotoxic oxidant peroxynitrite.

The following agents have been shown to reverse endothelial dysfunction: lipid-lowering drugs (HMG-CoA reductase inhibitors, probucol, cholestryramine), angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists (which inhibit the vasoconstrictor angiotensin II and its generation of superoxide anions as well as augment the endothelial vasodilator bradykinin), antioxidants (vitamin E, vitamin C, superoxide dismutase, probucol), folate, arginine, estrogen, nitrovasodilators, and prostacyclin analogs.

4. Mechanical factors

As the ventricle contracts, coronary flow is impeded by the compression of intramyocardial vessels. When coronary flow is measured with a flowmeter on the coronary artery, flow is as shown in **Figure 7**.

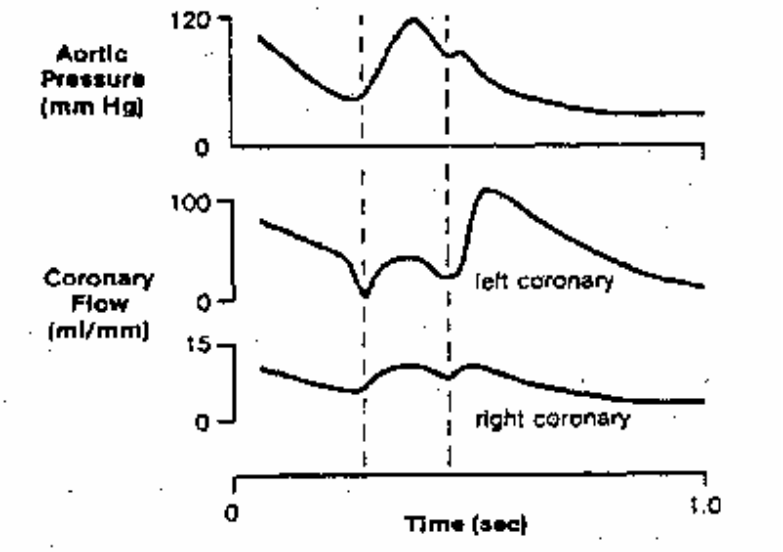


Figure 7

Right coronary flow is relatively less impeded than left coronary flow during systole because left ventricular systolic pressure is much higher than right ventricular systolic pressure.

The increased tissue pressure in the myocardium during systole is not evenly distributed across the wall. The pressure in the subendocardium is greater than that in the subepicardium. Thus, flow to the subendocardium occurs principally during diastole while the subepicardium is perfused throughout the cardiac cycle. Thus, it is the subendocardium which is first at risk when imbalances of blood supply and demand occur. Examples of this include severe tachycardia. In this situation oxygen demand is increased by the augmented heart rate, but since tachycardia shortens total diastolic time, the time for subendocardial perfusion is shortened. Metabolic vasodilation will compensate by decreasing coronary arteriolar resistance. However, when the tachycardia is excessive, compensation will be incomplete, and subendocardial ischemia will occur.

Another example of the greater risk to subendocardial muscle is seen in the presence of a coronary obstruction. Since perfusion of the subendocardium occurs only during a part of the cardiac cycle (diastole), decreases in flow induced by obstructive coronary lesions will be most prominent in the subendocardium.

5. Neural factors

Although coronary vessels are innervated by alpha and beta fibers, the importance of changes in sympathetic nerve activity is probably small. This is because of the overriding importance of changes in metabolic demand and the endothelium on coronary flow.

C. RELATIONSHIP BETWEEN DEMAND AND SUPPLY IN PATHOLOGIC STATES

Ischemic heart disease results from an imbalance between myocardial oxygen demand and supply. Assuming a normal oxygen-carrying capacity of the blood, an inadequate supply means an inadequate blood flow. Theoretically, this imbalance could occur when increased demand overwhelms the ability of a normal circulation to provide oxygen. This occurs in severe aortic stenosis. More commonly, a limitation of coronary flow is present (usually coronary atherosclerosis, rarely coronary spasm). Then, when myocardial oxygen demand increases above maximum possible oxygen supply, ischemia results. For example, increased demand provoked by exercise in the face of a limited coronary flow reserve (and thus, oxygen supply reserve) results in ischemia and symptoms of angina pectoris.

In the absence of obstructive coronary artery disease, autoregulatory mechanisms maintain a constant rate of coronary flow as long as the aortic perfusion pressure is ≥ 60 mm Hg. However, in advanced coronary artery disease, a fall in perfusion pressure distal to the coronary artery obstruction results in the accumulation of metabolites and maximal vessel dilatation with loss of flow regulation.

Thus, the aggravation or amelioration of ischemia in coronary artery disease depends on the following balance of clinically relevant factors:

Major Variables Controlling O_2 Demand:

Tension
Contractility
Heart Rate

Major Clinical Variables Affecting O_2 Supply

Patency of Coronary Arteries
Coronary Perfusion Pressure
Oxygen Content of Blood
? Coronary Collaterals

? Hemodynamic Factors - (myocardial tissue pressure, heart rate)

The clinical approach to patients with ischemic heart disease must always include consideration of the above. Since ischemia and infarction of the myocardium are produced by an imbalance between myocardial oxygen demand and myocardial oxygen supply, the therapy of ischemic heart is directed toward decreasing demand and increasing O_2 supply. Decreases in demand can be accomplished by decreasing myocardial tension, contractility, and/or heart rate. Increases in supply can be achieved with coronary angioplasty/stenting, coronary surgery, and possible pharmacologic agents.

III. Coronary Artery Collateral Circulation

Human coronary arteries are not "end arteries." Indeed, the terminal branches of coronary arteries are connected by microscopic vessels, termed "the collateral circulation." Collaterals may be intracoronary, connecting branches of the same artery, or intercoronary, connecting adjacent major arteries. Intercoronary collateral vessels, thought to be present at birth, range from 20 to 350 μm in diameter with average lengths of 1-3 cm.

Collaterals can increase in size in the setting of ischemia from a coronary obstruction or after coronary occlusion, particularly if the occlusion develops slowly over time. There is impressive variability in the importance of the collateral circulation from patient to patient. The collateral circulation is beneficial in the setting of coronary artery disease. For example, a well-developed collateral circulation despite severe coronary artery stenoses or occlusion of major coronary arteries may result in the absence of clinical expression of angina or infarction, and the preservation of normal left ventricular function. Moreover, the beneficial effects of coronary collaterals include:

1. Decreased infarct size,
2. Decreased left ventricular aneurysm formation after an infarct,
3. Increased left ventricular function after an infarct,
4. Increased long-term survival.

Chronic hypoxia, as seen in repeated ischemic events over time, and the presence of a

coronary artery pressure gradient owing to obstruction are major stimuli for collateral development. Angiogenic growth factors, including the fibroblast growth factors (FGF) and vascular endothelial growth factor (VEGF) promote collateral growth in a synergistic manner. Current clinical trials utilizing gene therapy with intramuscular injections of the naked plasmid DNA of the endothelial cell mitogen VEGF in patients with severe peripheral vascular disease and critical limb ischemia have demonstrated that VEGF can induce human artery collateral formation. Moreover, a recent study in which recombinant human FGF-1 was injected into the myocardium of patients undergoing multivessel coronary artery bypass surgery revealed neoangiogenesis and collateral formation within 12 weeks of treatment. Exercise and heparin may also stimulate collateral formation. Left ventricular hypertrophy with it attendant subendocardial ischemia is also thought to be a stimulus for collateral formation.

Collateral vessels are influenced by many of the agents that affect coronary artery vascular tone. Prostacyclin, nitric oxide (EDRF), nitroglycerin, and β-adrenergic stimulation all vasodilate the coronary collateral circulation. In contrast, the powerful platelet vasoconstrictors and platelet aggregatory agents, thromboxane A_2 and serotonin, as well as vasopressin and endothelin all vasoconstrict coronary collateral vessels.

IV. Coronary Artery Remodeling

The advent of the coronary artery intravascular ultrasound (IVUS) technique has shed light on the mechanisms underlying the ability of coronary arteries to remodel in atherosclerosis. Indeed, the vascular wall of the coronary artery may undergo a series of structural changes in response to the hemodynamic milieu. Remodeling of the coronary arteries includes vessel enlargement (outward remodeling) or vessel shrinkage (inward remodeling), and may either be compensatory or dysfunctional. The mode and degree of coronary arterial remodeling in response to a coronary artery stenosis is determined by endothelial cell production of cytokines, cellular adhesion molecules and proteases in response to sensed alterations in coronary arterial flow. In early atherosclerosis, compensatory enlargement of the diseased coronary artery will initially preserve the size of the coronary lumen. Although this adaptive mechanism is protective, the extracellular matrix degradation during remodeling may render the atherosclerotic plaque vulnerable to rupture, thereby leading to an acute coronary syndrome. In advanced atherosclerosis, coronary artery shrinkage may occur, thereby exacerbating the coronary artery stenosis. Coronary artery shrinkage has been implicated in both the restenotic process after balloon angioplasty and in the development of heart transplant coronary artery disease. Recent IVUS studies have demonstrated that cholesterol-lowering treatment in patients with coronary artery disease effects an in coronary lumen area that results not from a decrease in atherosclerotic plaque or stenosis size but rather from an increase in vessel area.

V. Inflammation and the Coronary Circulation

Inflammation has been implicated in the pathogenesis of atherosclerosis, particularly in the role of monocytes which adhere to lesion-prone arterial sites via endothelial cell adhesion molecules. Adherent monocytes enter the arterial intima and differentiate into lipid-rich macrophage foam cells. The latter process is facilitated by inflammatory modulators such as monocyte chemoattractant protein-1 and macrophage colony-stimulating factor.

In addition to playing a major role in the pathogenesis of atherosclerosis, inflammation plays a critical role in the pathogenesis of the acute coronary syndromes. Indeed, a large number of acute myocardial infarction patients have multiple complex unstable plaques associated with adverse clinical outcomes, thereby suggesting that inflammation may have widespread effects throughout the coronary vasculature. A recent study has demonstrated the presence of widespread activation of neutrophils across the coronary vascular bed in patients with unstable angina, regardless of the location of the culprit stenosis. This finding challenges the concept of a single vulnerable plaque which may cause an acute coronary syndrome by plaque rupture or erosion and is consonant with the current hypothesis that widespread coronary inflammation with multiple coexisting vulnerable plaques are present in acute coronary syndrome patients. An intravascular ultrasound study of patients with acute coronary syndromes has confirmed the presence of widespread coronary artery instability marked by multiple plaque ruptures throughout all three coronary arteries in addition to the culprit stenosis.

Future coronary events appear to correlate independently with increased circulating levels of a myriad of inflammatory markers including fibrinogen, serum amyloid A protein, interleukin-6, tumor necrosis factor α, adhesion molecules such as E-selectin and intercellular adhesion molecule-1, and C-reactive protein (CRP). Of these markers, the most extensively studied and most predictive inflammatory marker is CRP. CRP correlates with the progression of coronary artery disease, incidence of first myocardial infarction, and poor outcome in patients with unstable angina. Elevated CRP levels predict recurrent events in patients across the entire spectrum of acute coronary syndromes, independent of myocyte necrosis. CRP has also been implicated as having direct pro-atherothrombotic effects. CRP induces production of monocyte tissue factor, facilitates macrophage uptake of LDL, and directly induces human endothelial cell expression of vascular cell adhesion molecules in the presence of serum. Furthermore, CRP induces monocyte chemoattractant protein-1 in human endothelial cells, a proinflammatory effect which can be inhibited by a statin as well as a peroxisome proliferator-activated receptor α-activator. It should be noted that weight loss as well as both aspirin and statins have been shown to reduce CRP levels in patients, thereby reducing the risk of future cardiovascular events. A recent major study of 27,939 apparently healthy American women over a mean of eight years revealed that the C-reactive protein level is a stronger predictor of cardiovascular events than the LDL cholesterol.

Another important inflammatory prognostic marker is myeloperoxidase, an enzyme made by neutrophils and monocytes. In patients presenting to the emergency room with chest pain, a single initial measurement of plasma myeloperoxidase independently predicts the early risk of acute myocardial infarction and the risk of major adverse cardiac events in the ensuing 30 days and 6 months. Myeloperoxidase levels in contrast to troponin, creatine kinase MB isoform, and CRP levels, identified patients at risk for major adverse cardiac events in the absence of myocyte

necrosis. Myeloperoxidase oxidizes apolipoprotein A1 (apo A1), the major protein component of HDL, thereby potentially interfering with HDL's ability to effect reverse cholesterol transport. Myeloperoxidase also promotes lipid peroxidation and converts LDL into an atherogenic form, leading to macrophage foam cell production in atherogenesis.

VI. Pathophysiology of the Acute Coronary Syndromes

The acute coronary syndromes encompassing sudden ischemic death, acute myocardial infarction (MI), and unstable angina exact an enormous toll in the US each year in terms of mortality, morbidity, and economic cost. There are over 1.5 million hospitalizations for acute myocardial infarction and 1 million hospitalizations for unstable angina each year. There are 535,000 deaths each year from myocardial infarction, one death each minute, representing the leading cause of death in the US. The majority of MIs are non ST segment elevation MIs as opposed to ST segment elevation MIs. ST segment elevation MIs usually denote transmural infarctions and are usually associated with greater LV damage, a higher rate of MI expansion and remodeling, and a higher short-term mortality rate than non ST segment elevation MIs. Non ST segment elevation MIs may only have subendocardial damage and have a better short-term prognosis. However, non ST segment elevation MIs are more prone than ST segment elevation MIs to have recurrent infarction, and the long-term one year mortality is the same for ST segment elevation and non ST segment elevation MIs. Patients with non ST segment elevation MIs are more likely to have a depressed left ventricular ejection fraction and multivessel coronary artery disease than patients with ST segment elevation MIs.

Coronary arterial thrombosis is thought to play the leading role in the pathophysiology of the acute coronary syndromes. Mural thrombus, or clot within the arterial wall, contributes to pathogenesis of progressive coronary artery disease and stable, exertional angina.

However, an occlusive thrombus which either severely impedes or totally obstructs coronary flow occurs in unstable angina and acute myocardial infarction. Unstable angina includes angina at rest or on minimal exertion, post infarction angina, and non ST segment elevation myocardial infarction. Patients with unstable angina may present with: 1) more frequent, prolonged, or severe episodes of angina superimposed on a previous stable exertional angina pattern; 2) angina of new onset of one month occurring on minimal exertion; 3) angina either new onset or previously stable now occurring at rest or with minimal exertion.

In unstable angina (including non ST segment elevation myocardial infarction), there is a labile occlusive thrombus. In contrast, in a ST segment elevation myocardial infarction, there is a deeper, fixed occlusive thrombus which totally obstructs coronary flow for a longer period of time, resulting in more severe damage to the myocardium, and possible congestive heart failure or death.

The occlusive thrombus that forms in the acute coronary syndromes is the direct result of an atherosclerotic plaque rupturing or fissuring with exposure of the internal components of the plaque to the bloodstream, resulting in an intraluminal superimposed thrombus at the site of plaque rupture. In some cases of acute coronary syndromes, there is superficial plaque erosion followed by coronary thrombosis. Superficial plaque erosions are most often seen in younger individuals

and women and, compared to areas of plaque rupture, have less luminal narrowing, calcification, and inflammatory cell foci. The process of plaque rupture, superimposed thrombus formation, and possible lysis of the thrombus is a dynamic process. Autopsy studies have revealed several layers of clot of differing ages at sites of plaque rupture.

Coronary angioscopic studies of the acute coronary syndromes have revealed that lipid-rich yellow xanthomatous plaques that are ulcerated with ragged irregular surfaces are most likely to rupture. Moreover, the composition of the superimposed thrombus at the site of plaque rupture appears to differ in unstable angina versus acute ST segment elevation myocardial infarction. In unstable angina, there is white (platelet-rich) thrombus which is mural and non-occlusive. In contrast, in acute ST segment elevation myocardial infarction, there is red (fibrin-rich) thrombus which is occlusive.

Coronary angiographic studies have revealed that the vast majority of atherosclerotic plaques which rupture to cause unstable angina or acute myocardial infarction are angiographically small in size ($< 50\%$ stenosis). Moreover, the plaques that rupture have a much higher percentage of extracellular lipid owing to a higher density of lipid-rich macrophage foam cells and a greatly reduced percentage of vascular smooth muscle cells and their proteins (collagen, elastin, glycosaminoglycans), as compared to plaques that do not rupture. As a result, the plaques that rupture have a small thin cap secondary to the absence of smooth muscle cells and their proteins.

The law of Laplace determines the circumferential tension on the fibrous cap of an atherosclerotic plaque containing a lipid extracellular pool:

$$t = p \bullet r \qquad \sigma = \frac{p \bullet r}{h}$$

Tension (t) is related to the intraluminal pressure (p) and the luminal radius (r). Therefore, an angiographically smaller plaque with a larger luminal radius is more vulnerable to rupture. In addition, the mean circumferential stress (σ) on the fibrous cap is related to the circumferential tension and is inversely proportional to the thickness of the cap. Hence, angiographically small, lipid-rich, macrophage foam-cell laden atherosclerotic plaques with thin fibrous caps are most likely to rupture at the sites of highest circumferential biomechanical forces.

When plaques rupture, they rupture at the shoulder of the plaque, which is the point where the atherosclerotic plaque is adjacent to the normal endothelium. At the site of plaque rupture, within the atherosclerotic plaque, there is a high density of macrophage foam cells and T cells. The macrophage foam cells are harmful in two distinct ways. First, they secrete tissue factor which mediates the extrinsic pathway of coagulation resulting in the formation of thrombin and fibrin which contribute to the superimposed thrombus. HMG CoA reductase inhibitors have been shown to inhibit macrophage foam cell production of tissue factor. In addition, the macrophage foam cells release a series of enzymes called the matrix metalloproteases (collagenase, stromelysin, gelatinase, elastase) which degrade the thin cap exposing the lipid-rich, prothrombotic internal components of the plaque to the bloodstream, resulting in a superimposed thrombus. HMG CoA reductase inhibitors also inhibit macrophage foam cell release of matrix metalloproteases. Activated T cells in the shoulder of the plaque secrete interferon-gamma, an inhibitor of smooth muscle cell collagen synthesis and an inducer of smooth muscle cell apoptosis (programmed cell death). T cell production of interferon-gamma and expression of the CD40 ligand activate the

macrophage foam cells.

Collagen which is present in the atherosclerotic plaque causes platelets in the bloodstream to aggregate and form a clot. Moreover, macrophage foam cell tissue factor results in the formation of thrombin which is an extremely potent platelet agonist. The activated platelets adhere and aggregate at the site of rupture. Furthermore, aggregating platelets release thromboxane A_2 and serotonin which effect vasoconstriction at the site of rupture. Aggregating activated platelets are cross-linked by fibrinogen through the platelet glycoprotein IIb/IIIa receptor which also enables platelets to adhere to the endothelium via von Willebrand factor. Expression of the platelet glycoprotein IIb/IIIa receptor is the final common pathway of all platelet activation, and its expression is induced by any platelet agonist.

The mainstays of therapy for the acute coronary syndromes can be viewed in context of the underlying pathophysiology. Aspirin is a potent inhibitor of platelet cyclooxygenase and platelet aggregation which is used in the treatment of acute myocardial infarction, unstable angina, and stable angina. Primary balloon angioplasty/coronary stenting versus Thrombolytic therapy with either TNKase, tissue-type plasminogen activator (TPA), Retavase, or streptokinase is useful for an occlusive thrombus (red, fibrin-rich thrombus) which results in ST segment elevations on the EKG or a new left bundle branch block in an acute myocardial infarction. Primary balloon angioplasty/coronary stenting appears to be more efficacious than thrombolytic therapy, particularly if it can be performed within 90 minutes of a ST segment elevation MI patient appearing in an emergency room. The anticoagulant heparin is useful as an adjunct to thrombolytic therapy for acute myocardial infarction and is also front-line therapy for unstable angina. The low molecular weight heparin enoxaparin given subcutaneously has been shown to be efficacious in unstable angina and non ST segment elevation myocardial infarction. The combination of aspirin and clopidogrel, an inhibitor of ADP-induced platelet aggregation, is used to prevent subacute thrombosis after coronary artery stenting and also has efficacy in the acute and chronic treatment of acute coronary syndrome patients with unstable angina and non ST segment elevation myocardial infarction. The combination of aspirin and clopidogrel, (dual antiplatelet therapy), has also emerged as front-line therapy for all patients with STEM I, whether treated with primary angioplasty/stenting or thrombolytic therapy. Intravenous platelet glycoprotein IIb/IIIa receptor inhibitors (Abciximab, Eptifibatide, and Tirofiban) are useful as adjunctive therapy for coronary stenting and may be used for the treatment of high risk patients with unstable angina and non ST segment elevation myocardial infarction who will undergo percutaneous coronary intervention. Nitroglycerin is used to treat ischemic chest pain in stable angina, unstable angina, and acute myocardial infarction. Nitroglycerin dilates coronary vessels as well as the coronary collateral circulation, and is a potent venodilator. Intravenous nitroglycerin has anti-platelet properties. Beta-blockers reduce both the heart rate and blood pressure, reducing myocardial oxygen demand. Both nitroglycerin and beta-blockers are employed in the treatment of stable angina and unstable angina. Beta-blockers are also used in the acute treatment of acute myocardial infarction and for secondary prevention, i.e., to prevent a second myocardial infarction in a patient who has had a first myocardial infarction.

Finally, there is tantalizing evidence to suggest that vigorous cholesterol reduction with HMG CoA reductase inhibitors or statins resulting in LDL cholesterol levels < 70 mg/dl may be useful for secondary prevention of myocardial infarction in patients at risk. Vigorous cholesterol reduction may alter the cellular biology and plaque composition of the atherosclerotic plaque.

There is evidence from studies in primates as well as inferences from studies in humans that vigorous cholesterol reduction can render atherosclerotic plaques less vulnerable to rupture by removing macrophage foam cells and causing vascular smooth muscle cells to predominate and create a thick fibrous cap. One recent study TIMI 22-PROVE IT, demonstrated that aggressively lowering the mean LDL cholesterol to 62 mg/dl in patients with non ST segment elevation myocardial infarction and unstable angina by administering high dose atorvastatin (lipitor) – 80 mg po qd - resulted in a greater decrease in death and major cardiovascular events when compared to a less modest reduction to LDL levels of 95 mg/dl with pravastatin 40 mg po qd. Further analysis of the latter study has revealed that patients with low C-reactive protein (CRP) levels <2 mg per liter (significantly a lower inflammatory status) had better clinical outcomes than those with higher CRP levels >2 mg per liter, regardless of the resultant LDL level. Indeed, in the TIMI 22-PROVE IT trial, the patients who had LDL levels <70 mg/dl and CRP levels <1 mg/liter after statin therapy had the lowest rate of recurrent events.

In summary, the acute therapy for unstable angina as well as non ST segment elevation myocardial infarction includes:

1) aspirin
2) clopidogrel
3) heparin or low molecular weight heparin (enoxaparin)
4) beta-blockers
5) nitrates
6) statins (high dose)
7) intravenous glycoprotein IIb/IIIa inhibitors (high risk patients who will undergo percutaneous coronary intervention)
8) Patients should be taken to the Cath Lab for revascularization within 24-48 hours of presentation.

The acute therapy for a MI with ST segment elevation includes:

1) aspirin
2) clopidogrel
3) primary angioplasty/coronary stenting (90 minutes door – balloon time), if available, is superior to thrombolytic therapy (TNKase, TPA, Retavase, or streptokinase)
4) heparin, and
5) intravenous beta-blockers.

The long-term therapy after any acute coronary syndrome includes the secondary prevention measures of:

- aspirin
- clopidogrel
- beta-blocker (oral)
- statins (target LDL $<$ 70 mg/dl)
- angiotensin converting enzyme inhibitor (if a patient cannot tolerate an ACE inhibitor because of cough, an angiotensin receptor blocker may be substituted).

- epleronone, a selective aldosterone antagonist, should be considered if LVEF $< 40\%$ and the patient has clinical symptoms of CHF.

Coumadin is usually reserved for patients with an anterior wall MI who have developed a new LV aneurysm, apical mural thrombus, or have chronic atrial fibrillation or a severe cardiomyopathy.

Recently, the landmark Heart Outcomes Prevention Evaluation (HOPE) study revealed that ramipril, an angiotensin-converting enzyme inhibitor with tissue-specificity, significantly reduces the rate of death, myocardial infarction, stroke, heart failure, need for revascularization procedures, and the onset of and complications from diabetes mellitus in high risk vascular patients not known to have a low ejection fraction or heart failure.

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