CHAPTER II
LITERATURE REVIEW

Sedentary individuals with silent atherosclerosis might experience chest pain or heart attack when performing a vigorous exercise. Most heart attacks are associated with a blood clot blockage of the artery leading to a cardiovascular event. People with cardiovascular disease have an increased tendency to form blood clot (know as coagulate) and a decreased ability to dissolve clots (know as fibrinolysis) before they can do any damage. In addition to other risk factors and as age, high blood pressure, cholesterol levels, diabetes, smoking, obesity and genetics, impaired fibrinolysis also linked with the coronary artery disease (CAD).

2.1 Blood coagulation and fibrinolysis (Konler and Grant 2000)

The main coagulation reactions are divided into the intrinsic and extrinsic systems (Fig 2.1 left). Activation of factor XII on contract with a negatively charged surface initiates the intrinsic coagulation system. The extrinsic coagulation system induces the formation of a complex composed of factor VII and tissue factor, which is released after tissue injury. Some of these reactions depend on calcium ions. Thrombin is formed by an enzyme complex called prothrombinase, composed of factor X, factor V, negatively charged phospholipids, and calcium ions. Intrinsic and extrinsic activation of the coagulation cascade leads to the generation of thrombin of soluble fibrin, and finally, the formation of factor XIII-mediated, cross-linked, insoluble fibrin.

The main fibrinolytic reactions (Fig 2.1 right) involve the inhibition of fibrinolysis by plasminogen-activator inhibitor type 1 (PAI-1) and α_2-antiplasmin. Fibrinolysis is initiated by tissue plasminogen activator (t-PA), urinary-type plasminogen activator (u-PA), and plasmin. Plasmin bound to the

surface of fibrin initiates the lyses of insoluble, cross-link fibrin, with the subsequent generation of fibrin-degradation products. Plasmin bound to the surface of fibrin is better protected from inhibition by α_2-antiplasminthan is plasmin generated in fluid phase.

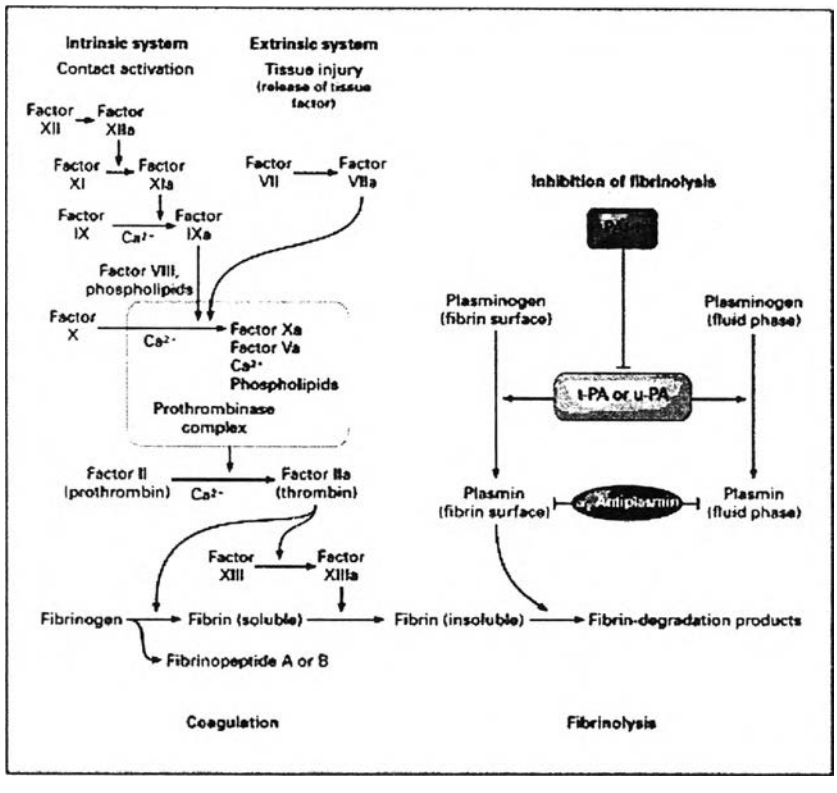


Figure 2.1 The Coagulation and Fibrinolytic Pathway (Kohler and Grant 2000)

Fibrinolytic system is an enzymatic system that is capable of dissolving blood clots. This system consists of many components (Table 2.1) which present as an inactive form in the circulatory system. For example inactive proenzyme (plasminogen) can be converted to be the active enzyme (plasmin). The activated enzyme will degrade fibrin into soluble fibrin degradation products. Two immunological as distinct types of physiologic plasminogen activators have been identified as t-PA and u-PA. Inhibition of the fibrinolytic system may occur either at 1) the level of the plasminogen activator inhibitor, by PAI-1 and PAI-2, or 2) the level of plasmin, by α_2-antiplasmin or α_2-macroglobulin.

TABLE 2.1. Physicochemical Properties of the Main Components of The Fibrinolytic System (Collen, Lijnen and Verstraete 1995)

	M_r(kd)	Carbohydrate Content (%)	No.Amino Acids	Plasma Concentration (mg/L)
Plasminogen	92	2	791	200
t-PA	68	7	530	0.005
scu-PA	54	7	411	0.008
α_2-Antiplasmin	70	13	452	70
α_2-Macroglobulin	725	8	4x1451	2500
PAI-1	52	-	379	0.05
PAI-2	47(60)	-	393	<0.005

2.1.1 Tissue Plasminogen Activator (t-PA)

t-PA is a serine protease of about 70 kd and composed of single polypeptide chain of 527 amino acids with Ser as NH_2-terminal amino acid (Collen, Lijnen and Verstraete 1995). It is the primary initiator of fibrinolysis in the vascular system where it plays an important role in regulating the formation and removal of thrombi.

The concentration of active t-PA in blood is to change in the synthesis and release of t-PA by the endothelium and to fluctuations in the liver blood flow, which influences the t-PA clearance by the liver. As the half-life of t-PA is very short, the t-PA concentration can vary rapidly. The production of t-PA comprises of two mechanisms: a constitutive of t-PA by the cells, and immediate release of t-PA from a storage pool in endothelial cells, which is induced by vasoactive substances, such as platelet activating factor,

bradykinin and thrombin (Emeis et al. 1996). This acute release mechanism plays an important role in the effective protection of blood against a locally emerging thrombus, because t-PA present during thrombus generation and incorporated in the thrombus is much more effective than when added after thrombus formation (Victor and Hinsbergh 1996).

Tissue plasminogen activation is strikingly enhanced by the presence of t-PA. The kinetic data support a mechanism where fibrin provides a surface to which t-PA and plasminogen adsorb in a sequential and ordered way, yielding a cyclic ternary complex. Fibrin essentially increases the local plasminogen concentration by creating an additional interaction between t-PA and its substrate. The high affinity of t-PA to plasminogen in the presence of fibrin thus allows efficient activation on fibrin clot, whereas no efficient plasminogen activation by t-PA occurs in plasma. Others, however, claim that fibrin influences both K_m and K_{cat} of plasminogen activation by t-PA.

Plasmin formed on the fibrin surface has both its lysine-binding sites and active site occupied and is only slowly inactivated by α_2-antiplasmin (half-life of about 10 to 100 s); free plasmin, when formed, is rapidly inhibited by α_2-antiplasmin (half-life of about 0.1s).

2.1.2 Plasminogen Activator Inhibitor-1 (PAI-1)

PAI-1 is a single-chain glycoprotein of about 52 kd consisting of 379 amino acid. In healthy individuals, highly variable plasma levels of both PAI-1 activity and antigen were observed. PAI-1 activity ranges from 0.5 to 47 IU/ml. PAI-1 antigen in plasma ranges between 6 to 85 ng/ml (Kruithof et al. 1988). PAI-1 binds rapidly to t-PA forming a stable complex with a ratio 1:1 (Lindahl et al. 1990). The active form of PAI-1 is unstable, with a half-life of 30 minutes (Kooistra et al. 1986). Activated PAI-1 is synthesized in platelets as well as endothelial cells (Sprengers et al. 1986; Kooistra et al. 1986)

Influence of Glucose and Insulin on the Production of PAI-1

Both glucose and insulin increase the synthesis and secretion of PAI-1 in human vascular endothelial and smooth muscle cells in vivo (Maiello et al. 1992; and Pandolfi et al. 1996). Studies of the promoter region of the PAI-1 gene have shown that hyperglycemia stimulates transcription of the gene just upstream from the transcription of start site (Chen et al. 1996). Thus, a reduction in the blood glucose concentration would be expected to result in reduced transcription of the PAI-1 gene and increased fibrinolytic activity in vascular tissue.

Control of hyperglycemia decreases plasma PAI-1 activity in patients with type 2 diabetes (Jain et al. 1993). Insulin treatment suppresses the secretion of both insulin and insulin precursor molecules, such as pro insulin and 32-33 split pro insulin, and leads to reduced plasma PAI-1 activity. Both pro insulin and split pro insulin have a marked effect on PAI-1 mRNA expression in porcine aortic endothelial cells, suggesting that not only insulin but also pro insulin-like molecules may have a role in regulating the synthesis of PAI-1 (Schneider et al. 1992). In addition, in patients with type 2 diabetes, insulin therapy results in a greater reduction in plasma PAI-1 concentrations than does sulfonylurea therapy (Panahloo et al. 1998).

Influence of Estrogen on the Production of PAI-1 (Gebara et al. 1995)

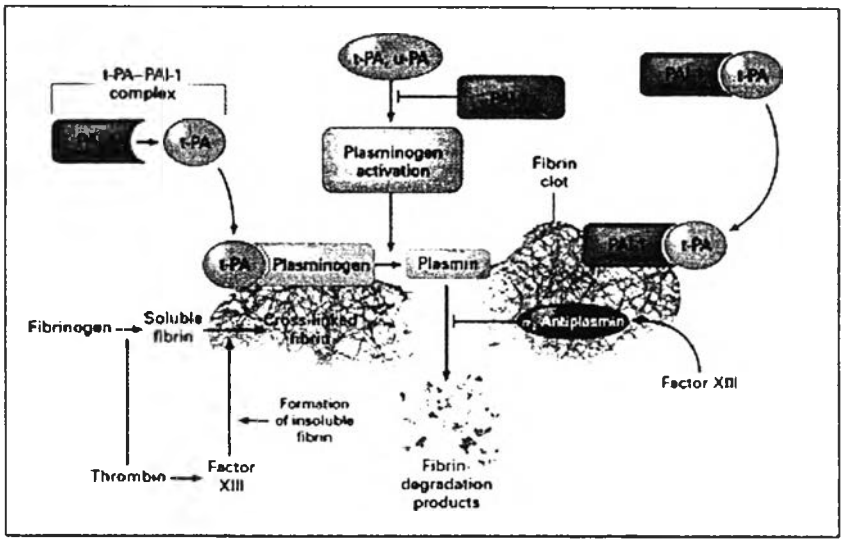
Postmenopausal women receiving estrogen-replacement therapy have lower plasma PAI-1 concentrations than those not receiving such therapy. In addition, premenopausal women have lower plasma PAI-1 concentrations than postmenopausal women. The presumed cardioprotective effect of estrogen in premenopausal women may be mediated, in part, through an increase in fibrinolysis.

The Renin-Angiotensin System and PAI-1 (Kohler and Grant 2000)

Activation of the rennin-angiotensin system is associated with an increased risk of ischemic events (Alderman et al. 1991). Angiotensin II stimulates the production of PAI-1 in cultured endothelial cells and vascular smooth muscle cells (Vaughan et al. 1995), whereas the inhibition of angiotensin-converting enzyme is associated with a decrease in both plasma PAI-1 concentrations and PAI-1 activity (Brown et al. 1999). These finding suggest one mechanism by which angiotensin-converting enzyme inhibitors may limit the progression of cardiovascular disease.

2.1.3 Interaction of PAI-1 and t-PA with Fibrin (Kohler and Grant 2000)

Since fibrinolytic reaction take place on the surface of the fibrin clot, fibrinolysis is restricted and does not become systemic. Plasminogen, t-PA, and fibrin form ternary complex (Fig 2.2) that promotes the formation of plasmin and the subsequent lyses of fibrin. Plasmin and t-PA are protected from inactivation by their respective inhibitors, α_2-antiplasmin and PAI-1. However, PAI-1 also binds to fibrin, and when bound, it retains its inhibitory activity against t-PA and urinary-type plasminogen activator. The binding of t-PA to fibrin may in part explain the inhibitory effect of PAI-1 on fibrinolysis. The incorporation of monoclonal antibodies against PAI-1 in a forming thrombus increase the rate of fibrinolysis and reduces the extension of the thrombus, suggesting that PAI-1 promotes the stability and extension of the clot. After it has been activated in platelets, PAI-1 is fixed within the clot by binding to fibrin and retains its capacity to inhibit u-PA and t-PA, increasing the clot's resistance to lysis. In the circulation, most t-PA is bound to PAI-1, although a small proportion is either free or bound to fibrin.



Figture 2.2 Activation and Inhibition of Fibrinolytic Pathway (Kohler and Grant 2000).

The inhibition of t-PA by PAI-1 is decreased by 80 to 90 percent in the presence of fibrin, because both thrombin-cleaved fibrinogen and fibrin reduce both PAI-1 activity. The latter process may be due to impaired access of PAI-1 to the catalytic domain of fibrin-bound t-PA. Since polymerized fibrin has a more complex structure than fibrin monomer, the accessibility of t-PA to fibrin is probably decreased. According to this model, t-PA increase fibrinolysis during the early stages of fibrin formation on ruptured arteriosclerotic plaques, whereas fully for red fibrin, which is highly polymerized and cross-linked, is resistant to fibrinolysis mediated by t-PA.

2.1.4 Fibrinolysis in Coronary Artery Disease (Kohler and Grant 2000)

The importance of the fibrinolytic system as a regulator of fibrin deposition in the vessel wall raises the question of the role of perturbations in this system in the development of vascular disease. In theory, at least, a decrease in fibrinolysis due to high plasma PAI-1 concentrations might be expected to result in an increase in the deposition of fibrin and subsequent

formation of a thrombus. High plasma PAI-1 concentrations are indeed associated with various thrombotic disorders and are an independent risk factor of reinfarction in patients who have had a first myocardial infarction before the age of 45 years. There is an association between the presence of coronary artery disease and low plasma fibrinolytic activity due to increase plasma PAI-1 concentrations.

In the prospective Northwick Park Heart Study, there was a strong, long-term relation between a low level of plasma fibrinolytic activity at enrollment and the subsequent incidence of coronary artery disease in young men, suggesting that low fibrinolytic activity precedes heart disease. In the prospective, multi-center European Concerted Action on Thrombosis and Disabilities study, high plasma levels of PAI-1 activity and antigen were associated with subsequent coronary events in patients with angina pectoris, but this association disappeared after adjustment for factors reflecting insulin resistance, such as the body-mass index and serum triglyceride and cholesterol concentrations. In addition, in a nested case-control study involving a northern Swedish population with a high prevalence of coronary artery disease, high plasma PAI-1 concentrations predicted the occurrence of a first acute myocardial infarction. In addition, a genetic polymorphism in the promoter region of the PAI-1 gene has been associated with both high plasma PAI-1 concentration and unstable angina.

Atheromatous material obtained at the time of coronary atherectomy in patients with type 2 diabetes mellitus contains more PAI-1, as detected by immunohistochemical studies, than atheromatous material from patient diabetes. Similarly, levels of PAI-1 messenger RNA (mRNA) are higher in severely are higher in severely atherosclerotic arteries than in normal arteries. These finding indicate that increased expression of the PAI-1 gene in the

arterial wall, leading to increased amounts of PAI-1 in plaques, may facilitate thrombotic events after the plaques rupture.

Integrins and other adhesion receptors that act as effector molecules in vascular remodeling initiate the attachment and spreading of endothelial cells, proteoglycans, and proteases, in particular, the plasminogen activator-plasmin system. During wound healing, the expression of u-PA and integrins, including $\alpha_v\beta_3$ integrin, is increased in migrating cells such as endothelial, smooth muscle, and blood cells.

The component of fibrin clots that stimulates cell migration is vitronectin, plasma and extracellular matrix protein that binds to endothelial cells through the receptor for urinary-type plasminogen activator. The fact that PAI-1 inhibits this reaction, thus blocking cell migration, suggests a direct link between plasminogenn activators and cell migration mediated by integrin and vitronectin. These finding are supported by the observation that wound healing and the formation of arterial neointima after injury are accelerated in mice with a deficiency of PAI-1. Thus, PAI-1 has an important role in vascular remodeling that is independent of its role as an inhibitor of t-PA.

Thus the fibrinolytic system in general, and PAI-1 in particular, having a role in the development of coronary artery disease is supported by the biologic characteristics of PAI-1 and the association between high plasma PAI-1 concentrations and other cardiovascular risk factors. Plasma concentrations of PAI-1 are lower during the day than at night, and it has been proposed that the higher incidence of myocardial infarction in the early morning hours could be due to higher plasma PAI-1 concentrations, and therefore lower fibrinolytic activity, at night (Angleton et al. 1989).

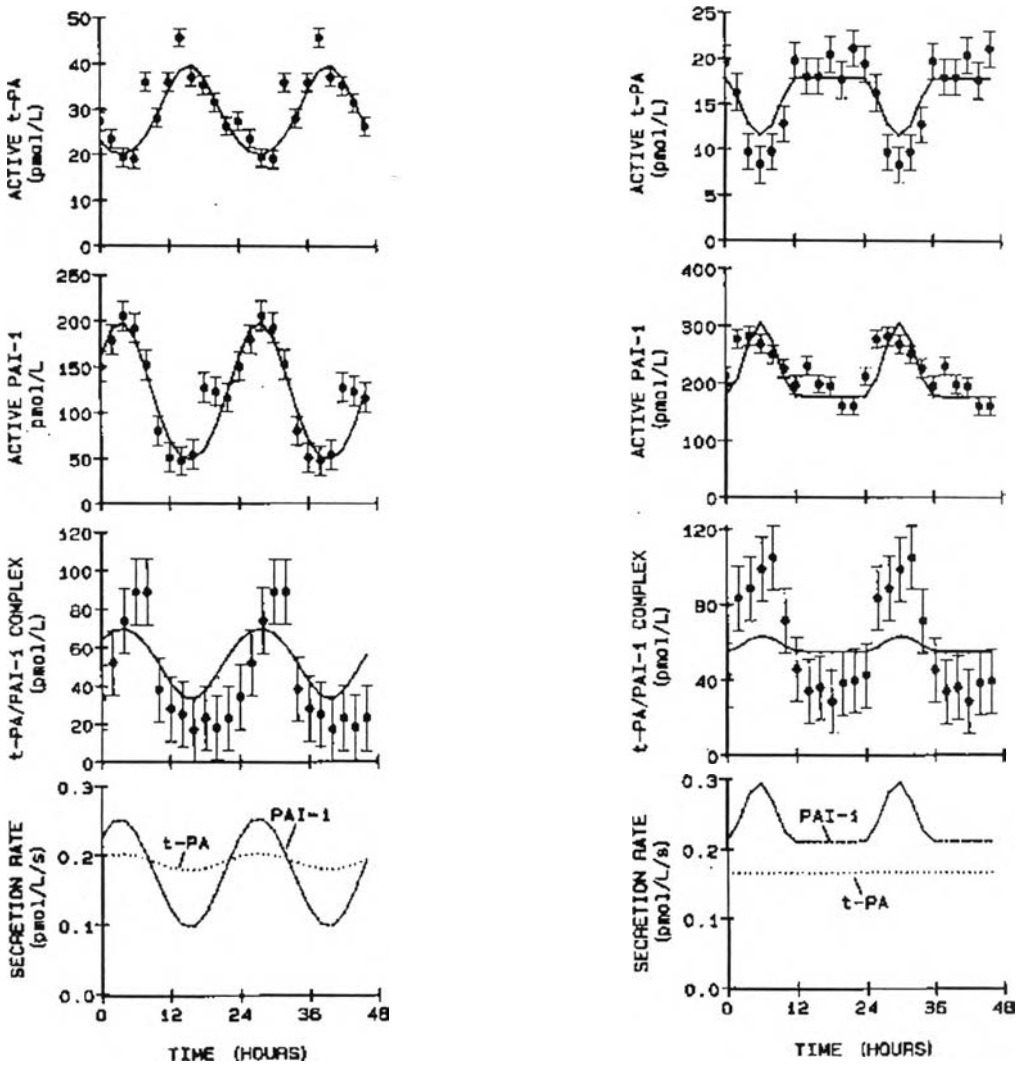


Figure 2.3 Diurnal Change of Fibrinolytic

(http://depts.washington.edu/labweb/dept/staff/bios/hemostas/)

The top three graphs in each column show a comparison between the measured (●) and best-fit simulated (-) values for active t-PA, active PAI-1, and t-PA/PAI-1 complex over 24 h for one subject. The bottom graph shows the predicted secretion pattern for PAI-1 and t-PA. This pattern is approximately sinusoidal for the subject whose data are represented on the left column; the pattern for the subject on the right column is characterized by a single peak in PAI-1 secretion in the morning. The data have been plotted twice to aid in evaluation.

Many important risk factors for coronary artery disease have been identified, including overweight, smoking, a sedentary lifestyle, dislipidemia, hypertension, and diabetes mellitus. A clustering of these factors is associated with an exponential increase in the risk of cardiovascular disease. In 1983, Reaven proposed the existence of a syndrome of insulin resistance in which the clustering of cardiovascular risk factor occurs more often than would be expected by chance alone. The main feature of this syndrome is insulin resistance accompanied by hyperinsulinemia, impaired glucose metabolism, hypertriglyceridemia with low serum high-density lipoprotein cholesterol concentrations, obesity, and hypertension.

2.2 Coronary Artery Disease (CAD)

CAD is Coronary Artery Disease, which is also known as ischemic heart disease. The cause of this disease is narrowing or blockage of one or more of the coronary arteries resulting in decreased blood supply to the heart. Narrowed artery accumulates by fatty deposits in the lining of arteries, resulting in low blood supply to the heart which could be fetal. CAD most often results from a condition known as atherosclerosis, which happens when a waxy substance forms inside the arteries that supply to the heart. This substance, called plaque, is made of cholesterol, fatty compounds, calcium, and a blood-clotting material called fibrin. There are 2 kinds of plaque: hard and soft, hard plaque can cause a heart attack. If hard plaque builds up in the arteries that supply blood to the heart, the blood flow slows or stops. This decreases the amount of oxygen that gets to the heart, which can lead to the heart attack.

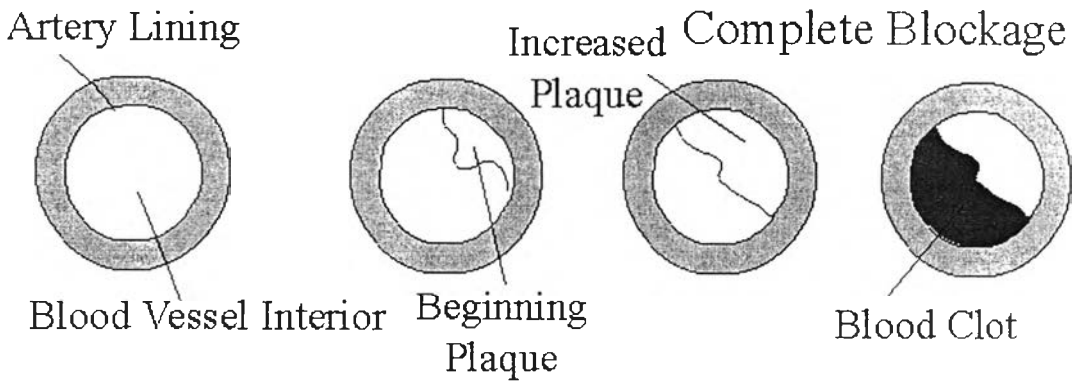


Figure 2.4 Process of coronary artery narrowing by plaque and blood clot.

2.2.1 Risk factors for CAD. (Killian and Joseph 1998)

Traditional risk factors are common place in patients with CAD. Their absence in many patients with vascular disorder provides a stimulus to search for other abnormalities that may also confer an increased risk of atherosclerosis. Several such abnormalities received more widespread attention recently as their possible roles in the genesis of atherosclerosis and thrombosis become more event.

- Homocysteine
- Lipoprotein
- Fibrinogen
- PAI-1

2.2.2 Diagnosis of CAD

Both invasive and non-invasive measures were used as tools for the diagnosis of CAD. They are as following:

- Electrocardiogram
- Exercise stress test
- Exercise thallium test

- Echocardiography
- Cardiac angiography
- Positron emission temography (PET) scanning

2.2.3 Treatment of CAD

Like other chronic disease, CAD can be treated in many methods depend on the timing of diagnosis and the severity of disease.

I. Medication (Opie 2001)

1. Antianginal Agents
    - Beta-Blocking Agents
    - Calcium Channel Blockers
    - Nitrates
2. Antifailure Agents
    - Diuretics
    - Angiotensin-Converting Enzyme (ACE) Inhibitors
    - Aldosterone Antagonism
    - Digitalis, Acute Inotropes, and Inotropic Dilators
3. Other Cardiac Drugs
    - Antihypertensive Drugs
    - Antiarrhythmic Drugs
    - Antithrombotic Agents: Platelet Inhibitors, Anticoagulation, and Fibrinolytics
    - Lipid-Lowering and Antiatherosclerotic Drugs

II. Transcatherter interventions

When the blockage of coronary vessel is exceeding the capacity of heart to perform the normal function, the transcatheter interventions are introduced as follows:

- Angioplasty, Percutaneous transluminal coronary angioplasty (PTCA), Stent
- Atherectomy
- Laser ablation
- Percutaneous transmyocardial revascularization

III. Surgery

In the most severe cases when the damage is beyond repaired by the above mentioned measures, patients are obligate to receive open heart surgery i.e. coronary artery bypass graft (CABG).

2.4 Cardiac Rehabilitation (Wenger et al. 1999)

Cardiac rehabilitation is a combination of services that helps patients with cardiovascular disease improve their functional abilities, particularly their tolerance for physical activity; decrease their symptoms; and achieve and maintain optimal health. Cardiac rehabilitation services are comprehensive, long-term programs involving medical evaluation, prescribed exercise, cardiac risk factor modification, education, and counseling. These programs are designed to limit the physiological and psychological effects of cardiac illness, reduce the risk for sudden death or reinfarction, control cardiac symptoms, stabilize or reverse the atherosclerotic process, and enhance the psychosocial and vocational status of selected patients.

2.4.1Components of the Exercise Session (Franklin and Fowler 1999; Tobin 1999)

Exercise training session should include a preliminary warm-up (10 min), a cool-down (5 min). A conditioning phase (30-60 min of continuous or accumulated activity), interspersed between the warm-up and cool-down,

should involve aerobic-endurance exercise and, for selected patients, a resistance training period .

Warm-Up

The warm-up prepares the body for more intense activity by stretching the large muscle groups and gradually increasing blood flow. Moreover, a preliminary warm-up serves to decrease the susceptibility to injury and the occurrence of ECG abnormalities that are suggestive of myocardial ischemia and/or ventricular electrical instability-abnormalities that may be elicited by sudden strenuous exertion. Thus, warm-up has preventive value and enhance performance capacity.

Cool-Down

The cool-down permits appropriate circulatory readjustments after vigorous activity; enhances venous return, thereby reducing the potential for post-exercise lightheadedness; facilitates the dissipation of body heat; promotes more rapid removal of lactic acid than stationary recovery; and combats the potential deleterious effects of the post-exercise rise in plasma catecholamine. Omission of a cool-down in the immediate post-exercise period may result in a transient decrease in venous return, possibly reducing coronary blood flow when heart rate and myocardial oxygen demand may still be high.

Intensity

The prescribed exercise intensity should be above a threshold level required to induce a training effect, yet below the metabolic load that evokes abnormal signs or symptoms. For most deconditioned cardiac patients, the minimal intensity for exercise training is probably between 40 and 60% VO_{2max};

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however, considerable evidence suggests that it increases in direct proportion to the baseline aerobic fitness or level of habitual physical activity.

Measurement of Exercise Intensity

Intensity of exercise determines the total caloric expenditure during a training session. Training induced physiological change depends on the intensity of overload. There are at least seven ways to express exercise intensity.

1. As calories expended per unit time.

2. As particular absolute exercise level or power output

3. As a level of exercise below at, or above the lactate threshold (i.e., 4 millimole lactate)

4. As particular relative metabolic level expressed as a percentage of VO_{2max}

5. As particular exercise heart rate or percentage of maximum heart rate

6. As multiple of resting metabolic rate (MET is metabolic equivalent, a unit used to estimate the metabolic cost (energy expenditure as reflected by oxygen consumption) of physical activity, One MET equates the resting metabolic rate, which is approximately 3.5 milliliters of oxygen per kilogram body weight per minute. METs are used to compare the energy costs of different activities).

7. As some rating of perceived exertion (RPE) from 6 (very, very light) to 19 (very, very hard).

Rating of Perceived Exertion

The rating of perceived exertion (RPE) is a useful and important adjunct to heart rate as an intensity guide for cardiac exercise training, Exercise rated as 11 to 13 (6-20 scale) or 3 to 4 (0-10 scale), between" fairly light" and

"somewhat hard" (6-20 scale), or between "moderate" to "somewhat strong" (0-10 scale), generally corresponds to the upper limit of prescribed training heart rate during the early stages of outpatient cardiac rehabilitation. Later, for higher levels of training, ratings of 12 to 14 (6-20 scale) or 4 to 5 (0-10 scale) may be appropriate, corresponding to 70% to 85% of the HR_{max} which is equivalents to ~60 to 80% VO_{2max}. Although the RPE correlates well with exercise intensity, even in patients whose heart rates are attenuated by beta-blockade, ischemic ST segment depression and threatening ventricular dysrhythmias can occur at low levels of perceived or physical effort.

2.4.2 Frequency and Duration of Training

Improvement in VO_{2max} with low-to-moderate training intensities suggests that the interrelation among the training intensity, frequency, and duration may permit a decrease in the intensity to be partially or totally compensated for by increases in the exercise duration or frequency, or both. Regular exercise training for 10 to 15 min may improve cardiorespiratory fitness, and 30-45 min sessions are even more effective. Moreover, recent studies suggest that longer exercise sessions can be accumulated in shorter periods of activity (i.e., three 10-or 15 min exercise bouts). Although cardiac patients may respond to slightly less than twice-weekly exercise, three or four evenly spaced workouts per week appear to represent the optimal training frequency. Thus, relative increases in functional capacity appear to depend more on the patient's initial fitness and total amount of exercise accomplished or calories expended than on the specific exercise frequency, intensity, or duration.

A recent American Heart Association consensus statement on preventing heart attack and death in patients with coronary disease extolled the importance of a minimum of 30 to 60 min of moderate-intensity activity

three or four times weekly supplemented by an increase in daily lifestyle activities.

2.4.3 Exercise Prescription for Cardiac Patients

Stratification for Risk of Exercise-Related Cardiac Events

Information from the initial evaluation should be used to identify contraindications to exercise training and design a safe, effective exercise prescription. There are certain individuals for whom the risks of exercise training may outweigh the potential benefits (Table 2.2).

Table2.2 American Association for Cardiovascular and Pulmonary Rehabilitation Risk Stratification Model: Stratification for Risk Event

Lower Risk
No significant LV dysfunction (EF>50%)
No resting or exercise-induced complex dysrhythmias
Uncomplicated MI, CABG, angioplasty, atherectomy, or stent: absence of CHF, absence of signs/symptoms indicating postevent ischemia
Normal hemodynamic with exercise or recovery
Asymptomatic including absence of angina with exertion
Functional capacity ≥ 7.0 METs
Absence of clinical depression
Lower risk classification is assumed when each of the risk factor in the category is present.
Moderate Risk
Moderate impaired left ventricular function (EF = 40-49%)
Signs/symptoms including angina at moderate levels of exercise (5-6.9 METs) or in recovery.
Moderate risk is assumed for patient who do not meet the classification of either highest -risk or lowest risk.

Table2.2 American Association for Cardiovascular and Pulmonary Rehabilitation Risk Stratification Model: Stratification for Risk Event

Highest Risk
Decreased LV function (EF<40%)
Survivor of cardiac arrest or sudden death
Complex ventricular dysrhythmia at rest or with exercise
MI or cardiac surgery complicated by cardiogenic shock, CHF and/or signs/ symptoms of post procedure ischemia
Abnormal hemodynamics with exercise (especially flat or decreasing systolic blood pressure or chronotropic incompetence with increasing workload)
Signs/symptoms including angina pectoris at low levels of exercise (<5.0 METs) or in recovery
Functional capacity <5.0 METs
Clinically significant depression
Highest risk classification is assumed with the presence of any one of the risk factors included in this category.

Contraindications to participation in outpatient cardiac rehabilitation exercise training are listed in Table 2.3. Exceptions should be considered based on sound clinical judgment.

Table 2.3 Contraindications to Outpatient Cardiac Rehabilitation Exercise Training

1. Unstable angina
2. Resting SBP >200 mmHg or resting DBP >110 mmHg should be evaluated on a case-by-case basis
3. Orthostatic blood pressure drop of >20 mmHg with symptoms
4. Critical aortic stenosis (peak systolic pressure gradient > 50 mmHg with aortic valve orifice area <0.75 cm^2 in average size adult)

5. Acute systemic illness or fever
6. Uncontrolled atrial or ventricular arrhythmias
7. Uncontrolled sinus tachycardia (> 120 beats/min)
8. Uncompensated CHF
9. 3^{o}AV block (with out pacemaker)
10. Active pericarditis or myocarditis
11. Recent embolism
12. Thrombophlebitis
13. Resting ST segment displacement (>2 mm)
14. Uncontrolled diabetes (resting blood glucose > 400 mg/dL)
15. Severe orthopedic problems that would prohibit exercise
16. Other metabolic problems, such as acute thyroiditis, hypo-or hyperkalemia, hypovolemia, etc.

Components of outpatient exercise training

The intensity of exercise is set at approximately 50 to 60% of exercise capacity, using either a target heart rate based on a symptom limited graded exercise test or with perceived exertion levels of 11 to 14.

Table2.4 Intensity of Exercise as a Function of the Percentage of Maximal Heart Rate and Maximal Oxygen Uptake, and Ratings of Perceived Exertion (RPE).

$\%HR_{max}$	$\%VO_{2max}$	RPE	Intensity classification
<35	<30	<10	Very light
35-59	30-49	10-11	Light
60-79	50-74	12-13	Moderate
80-89	75-84	14-16	Heavy
>90	>85	>16	Very heavy

The duration of exercise begins conservatively, usually 10 to 15 min per session, with a gradual increase to 30 to 45 min by third week. The exercise may be performed continuously for the desired duration using a single mode of activity, or multiple modes of activity. The exercise session may also employ interval training, which uses periods of higher intensity exercise alternated with periods of lower intensity activity. This approach is particularly effective in rapidly improving exercise capacity. Although not commonly employed in coronary patients, it has been demonstrated to be effective for patients with chronic heart failure. Some patients with extremely poor exercise capacities or those limited by symptoms of claudication cannot exercise for more than a few minutes initially. Intermittent exercise is helpful for these patients.

Table 2.5 Intermittent Exercise Progession Suggestions for Patients with Extremely Poor Exercise Capacities (EC, <3 METs)

Week	%EC	Total min @%EC	min Exercise	min Rest	Reps
1	40-50	10-15	3-5	3-5	3-4
2	40-50	12-20	5-7	3-5	3
3	50-60	15-25	7-10	3-5	3
4	50-60	20-30	10-15	2-3	2
5	60-70	25-40	12-20	2	2

Frequency of exercise is set at 4 to 6 days per week; up to three sessions per week may be in a supervised environments. Walking and ergometry are the most common modes of exercise during the first several weeks.

The exercise sessions must begin with a series of warm-up activities to prepare the musculoskeletal system for the conditioning exercise phase and to increase cardiac output as well as blood flow to the myocardium. This is accomplished by combination of static stretches for the major muscle groups, dynamic range of motion activities, and several minutes of low-level aerobic exercise. At the end of the conditioning period, a cool-down routine that consists of lower level aerobic activity, static stretching, and dynamic range of motion movements is performed. The stretching activities, especially when performed after a period of aerobic activity when the skeletal muscle temperature is elevated, are helpful in improving flexibility.

2.2 Effects of Exercise on Fibrinolytic System

Lin et al. 1999, studied effect of strenuous physical exercise and compare with activates blood coagulation and enhances fibrinolytic activity. To investigate whether these activations of blood coagulation and fibrinolysis are balanced post exercise and during the period of recovery, 11 moderately active young men were examined immediately after a standardized cycle ergometer test at 75%VO_{2max} and during the 24 h period of recovery. Blood samples were obtained at rest, immediately after exercise, and 2, 6 and 24 h after exercise. Exercise induced a significant increase in factor VIII activity and this occurred with a significant shortening of activated partial thromboplastin time. A concomitant enhancement of t-PA resulted in significant increase in tissue t-PA antigen and total fibrin/fibrinogen degradation products, and significant decrease in PAI-1 activity. Increase in coagulation and fibrinolytic activity changed in parallel during exercise. However, during recovery, while the increase in factor VIII activity post exercise persisted 2 and 6 h into recovery, fibrinolytic activity demonstrated a sharp fall. It is concluded that whereas the enhanced fibrinolytic activity during exercise appears to

counterbalance the increase in blood coagulability, this perturbed blood haemostasis balance is not maintained during recovery. This perturbed blood haemostasis could constitute an enhanced risk for coronary artery thrombosis.

Hegde et al. 2000, was to evaluate and compare the change in blood clotting and fibrinolytic activity during the 1-h period after a submaximal run of similar relative exercise intensity in young men. Change in clotting and fibrinolytic activity were assessed by measuring several factor (APTT, factor VIII activity, t-PA antigen, and D-Dimer) every 20 min during the 1-h post exercise period (70-75%VO_{2max}).The results of this study indicated that there was an activation of both clotting (decrease APTT and increase FVIII activity) and fibrinolytic (increase t-PA antigen) activity for 1 h after a 30 min submaximal run at 70-75%VO_{2max} as compared with a 30 min walk at 1.2 mph in young male subjects. The increased D-Dimer level suggest that there was an activation of fibrin and its turnover. It is important to note that t-PA antigen levels declined over the 1-h period after the run, whereas the clotting activity activation was sustained. These findings suggested that changes in fibrinolytic activity and clotting activity were not balanced during the 1-h period after the run. This could favor clot formation, as indicted by increased D-Dimer, that may trigger cardiac incidents like AMI and sudden cardiac death in individuals prone with diseased vascular beds.

DeSouza et al 1997, study the fibrinolytic response to an acute bout of moderate physical activity (walking on treadmill at 65%VO_{2max}) in sedentary older hypertensive men. There were no significant differences between the hypertensive and normotensive groups in the time course and magnitude of change in either t-PA antigen or t-PA activity in response to 30 min bout of submaximal exercise. However, 30 min after cessation of exercise, both t-PA antigen and t-PA activity had returned to pre exercise levels and were unchanged at 60 min post exercise in both groups. In both groups PAI-1

activity was lower immediately after exercise and remained lower than pre exercise levels for up to 1 h after exercise.

Womack et al. 2000, evaluation the fibrinolytic response to repetitive bouts of symptom limited exercise in peripheral arterial disease (PAD) patients. Fibrinolytic were obtained immediately after, 30 min after, and 60 min after submaximal treadmill walking at 65 %VO_{2max}.These findings demonstrated that repetitive bouts of symptom limited exercise produced a substantial improvement in the fibrinolytic profile of PAD patients, which persists at least 1 h after exercise cessation.

Paramo et al. 1998, study in AMI and healthy controls who underwent a cardiac rehabilitation program (9 months). There was a marked decrease of functional PAI-1 after 9 months as compared with baseline in AMI patients. The cardiac rehabilitation program improved fibrinolysis, by reducing the functional levels of PAI-1.

Table 2.6 Effect of Exercise on Fibrinolytic System

Author	Exercise program	Subjects	Findings
Schuit et al.1997	T, 6 mo	healthy elderly	PAI-1 decrease
		Men and women	t-PA increase
Paramo et al. 1998	T, 9 mo	CAD patients	PAI-1 decrease
			t-PA increase
Hegde et al. 2000	UT, submaximal	young men	t-PA change
	Run		
Lin et al.1999	UT, 70%VO_{2max}	young men	PAI-1 decrease
			t-PA increase
Desouza et al.1997	UT, 65%VO_{2max}	older hypertensive	PAI-1 decrease
			t-PA increase
Womack et al.2000	UT, 65% VO_{2peak}	PAD patients	PAI-1 decrease
			t-PA increase
Weiss et al.1997	UT, 70-85% VO_{2peak}	healty men	t-PA increase

* T = Trained, UT = Untrained