The effect of aerobic, resistance and concurrent exercise on some of the major blood homeostasis factors

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\section*{Abstract}

Recently, the disorder of the hemostasis system in relation to the clinical complications from cardiovascular diseases has become more recognized. The stability of the main coagulation and fibrinolysis factors has an important role in maintaining hemostasis. Activation of blood coagulation is associated with accelerated clot formation, whereas activation of blood fibrinolysis increases the breakdown of the blood clot. The effect of hormones and enzymes is a major factor in the fibrinolysis-coagulation balance and imbalance between them, leads to thrombosis. The type, intensity and duration of exercise in the hemostasis process are very important. Most coagulation factors are sensitive to intense exercises. In other hand, Most fibrinolysis factors are susceptible to long-term chronic sub-maximal exercises (over 1 hour) with intensity of 80-75 HR max. It can be concluded that the effect of aerobic exercise on coagulation and fibrinolysis factors has a significant effect when associated with weight loss. In short-term intense exercises, the effect of training on coagulation and fibrinolysis factors has been reported more than aerobic. In concurrent exercise, inter-lukin 1 response decreases, which is associated with the reduction of fibrinogen synthesis. Therefore, the role of intensity is greater than the duration, unless the duration of the training is high. So far, few studies are available related to the influence of exercise on blood coagulation and fibrinolysis and the exact effects of exercise training on the equilibrium between blood coagulation and fibrinolysis is not as yet known. It is necessary to perform different intensity and duration training protocols.

\section{1. Introduction}

The development of urbanization and inactive life style, increase the incidence and prevalence of non-communicable diseases (cardiovascular diseases, cancers, diabetes, stroke, etc.) and their risk factors (Khademi et al. 2011). Cardiovascular disease (CVD) is one of the most common causes of mortality in many countries as one of the most important health threats of the people (Khademi. 2004, 2007). Cardiovascular diseases not only have high morbidity but also have physical, psychological and social consequences for patients. Before we call a cardiovascular disease as disease, we need to know it as a syndrome, because most patients experience a variety of risk factors during their lifetime (Khademi et al. 2011). The prevalence of these diseases due to an increase in the prevalence of their risk factors has root in the people's lifestyle (Bobadilla et al.1993 ; Chockalingam 1999). CVD risk factors include lifestyle factors such as physical activity, diet, smoking and alcohol, and physiological and biochemical factors including increased blood pressure, weight, blood sugar, and cholesterol (Khademi 2004 & Noori, 2000). By eliminating any of the above factors, the risk of cardiovascular disease decreases (Mackay & Mensah, 2004). During the past 25 years, in industrialized countries, with changes in lifestyle, mortality from cardiovascular diseases has been decreased because of reducing fat intake and controlling tobacco, blood pressure, increasing physical activity and controlling other risk factors (Frank, 1995). However, in developing countries, the deaths from CVD have risen from 20% - 25% to 35-40% .This increasing is due to a tendency toward urbanization, reduced physical activity, obesity, increased blood lipids, and other hazardous risk factors (Mohammadi et al, 2002).
The most important cause of coronary artery disease is atherosclerosis. The pathological changes in atherosclerosis begin in childhood and occur in several stages at higher incidence (Jayachandran & Okano, 2004). Pathogenic changes in atherosclerosis progresses with age and eventually lead to disability and mortality in elderly age. One of the main challenges of atherosclerosis is the ability to measure clot formation and the process of fibrinolysis disorder. Most cardiovascular drugs act by changing the function of platelet, coagulation, or fibrinolysis, to prevent excessive clotting. In people with excess hemostatic imbalances that leads to over-coagulation, even partial rupture in the vein leads to excessive clotting. The first step in the prevention of bleeding is contraction of the damaged vessel, sometimes called vascular spasm (Smith, 2011). In the past decade, it has been determined that coagulation and fibrinolysis factors, as well as novel biomarkers, play an important role in the pathogenesis of chronic disease, including cardiovascular disease (Hansson, 2005). Also, in many studies, the role of local and general inflammation in the process of atherosclerosis and its related problems has been determined (Huffman, 2006). Coagulation and fibrinolysis parameters are very important as predictors of cardiovascular disease, independent of the common risk factors (traditional) (Ridker et al, 2003; Saify et al., 2017). Inflammatory, fibrinolysis and coagulation factors can disrupt the blood hemostasis.

2. Hemostasis: coagulation and fibrinolysis

Blood hemostasis represents a complex interaction between the coagulation and fibrinolysis systems, platelets, other circulating cells and the vascular wall. Blood coagulation is an important mechanism in the hemostatic system that involves a complex series of interactions between proteases, enzymes, and co-factors that lead to the generation thrombin and the formation of the fibrin-rich clot. Fibrin-rich clot formed at the end of the blood coagulation cascade, plays a temporary role and must be removed when normal tissue structure and functions are restored. The fibrinolysis system is the main mechanism designed for the clot removal and controls the enzymatic degradation of fibrin. The dominant mechanism for fibrinolysis in vivo is the plasminogen-plasmin system, which can be activated by intrinsic and extrinsic pathways (Bachmann et al. 1994 & El-Sayed, 1996).

Fibrinolysis and coagulation factors can disrupt the blood hemostasis. The main causes of cardiovascular disease are imbalances in the hemostasis system. The equilibrium of hemostasis refers to the dynamic balance between coagulation and fibrinolysis (Ridker et al. 2003). Cardiovascular diseases, such as infarction and heart attacks, are one of the major causes of death in adult populations (Bartsch, 1995 & Frank, 1995). In most cases, infarction occurs when the endothelium, which is usually anti-thrombosis, is torn and the clot is formed in the coronary artery. Moreover, thrombosis is irritated with plaque rupture and trap blood platelets and coagulation factors of the thrombosis in the wall of the arteries (Tofighee et al, 2015). This condition leads to the rapid formation of platelet mass, which is enhanced by fibrin and converted to a blood clot (thrombosis). Thrombosis leads to a reduction or complete stop of blood flow and death of myocardial tissue. In fact, physical activity and exercise has protective effects on the heart with a reduction of tendency to form clots and increase fibrinolysis power in recovery after exercise (Smith, 2011). Tissue plasminogen activator (t-PA), Plasminogen activator inhibitor type1 (PAI-1), fibrinogen, plasminogen and fibrin dimer are major coagulation and fibrinolysis factors in preserving hemostasis and preventing, diagnosing and treating many cardiovascular diseases. Despite their importance, to measure them, access to laboratory tools and methods is difficult and economically costly and time-consuming. These factors can be the cause of the deaths of many patients with cardiovascular disease (Smith, 2011). Although the effects of physical training on coagulation and fibrinolysis agents have been briefly investigated, available meagre evidence suggests that exercise training is associated with favorable effects on coagulation and fibrinolysis factor in both men and women. There are inadequate information on coagulation and fibrinolysis factors in exercise intensities, different age and sexes, and it is a need for exercise with varying intensity and concurrent training methods. On the other hand, there are few studies on the effects of concurrent, resistance and continuation training on factors such as t-PA, PAI1, Fibrinogen, Plasminogen, Fibrin dimer; PT and PTT in a single study, and the researches have provided contradictory results (Kupchak, 2013 & Leninger et al, 2013).

3. The effect of coagulation and fibrinolysis factors

Plasminogen activator (t-PA) and its inhibitor (PAI1) have been identified in several studies as risk factors for heart disease (Saify et al, 2011). By increasing the t-PA antigen in people with heart disease, including heart attack, if the PAI level increases in these patients, t-PA levels decreases (Saify & Piri, 2016). Two types of plasminogen activator have been identified in the human body, tissue type—Plasminogen activator (t-PA) and urine-type Plasminogen activator (Saify et al, 2017). The t-PA protein is a proteolysis enzyme found in blood and tissues. The major role of this enzyme is the production of plasmin that can dissolve blood clots in the heart and blood vessels. Recent studies have shown that reduction of t-PA activity and increased levels of PAI antigens are a risk to heart disease (Saify et al, 2017). Fibrinolysis is mainly initiated and released by the fibrin surface, which is the suitable site for optimum contact between a number of fibrinolysis system components, especially Plasminogen and t-PA. The stimulatory effect ensures high concentration of Plasminogen and t-PA in fibrin deposition and establishment of plasmin activity (Saify et al, 2018).

The inhibitory regulation is provided by PAI1 and plasmin inhibitor. The main inhibitor of t-PA, which has high efficiency, is PAI1 in plasma, and the major amount of t-PA in circulation is surrounded by this inhibitor. PAI1 is known to be a preventive for endothelial plasminogen, which encoded in humans as serine derivatives by the serpine gene. The rise in PAI1 rates leads to thrombosis and atherosclerosis. In normal condition, there is a fair balance between the fibrin formation and its subsequent degradation. However, in some conditions, pathogenicity and inherited defects, this equilibrium disappears. The inherited increase in fibrinolysis activity usually causes severe bleeding. Conversely, fibrinolysis reduction activity may lead to coagulation or blood clotting (Frank, 1995).

The central enzyme composition in fibrinolysis is plasminogen (a glycoprotein that is present in plasma and many exterior fluids) (Saify & Piri, 2015). Plasminogen is a zymogen from the serine proteases that after partial digestion by t-PA converts to its active form (Plasmin). Plasmin contributes to various pathways, including cell growth and mobilization, inflammation and tumor invasion, although its primary role is in the lyses or deterioration of
fibrin in the veins (Frank, 1995). The t-PA enzyme is predominantly secreted from the endothelial cells into the plasma (Kristensen et al. 1984). Different regions of the arteries produce different amounts of t-PA (Schrauwen et al. 1994). There are two forms of t-PA, single chain and two chains. The single chain is the natural form of t-PA secreted from endothelial cells, while the two-chain form is the result of plasminogen proteolysis activity. Both forms have similar enzymatic characteristics in the presence of fibrin (Saify et al. 2011).

In the absence of fibrin, the t-PA enzyme is relatively a weak plasminogen activator, because with a relatively low tendency binds to plasminogen. While t-PA have a high affinity to fibrin and t-PA binding to the fibrin increases the capacity of t-PA activation more than 1,000 times (Saify et al. 2009). This increase is related to the specific binding sites on the fibrin surface that increase the concentration and appropriate direction of t-PA on the substrate, which ultimately results in high blood clotting lysis (Nieuwenhuizen, 1994).

Epoxyeicosatrienoic acids (EETs) are important dilatation products Cytochrome P450 epoxygenases, and cause repolarization of the heart- muscle cellular. EET has anti-inflammatory properties through inhibition of NF-kB neurotransmission. Also, EET has numerous effects on the vascular wall in addition to vascular dysfunction (Koichi et al., 2001). Therefore, EETs play an important role in regulating vascular hemostasis. The EET molecules are attached to the receptor in the endothelial cell wall, which ultimately activates and produces cAMP. By increasing cAMP concentration in the cytoplasm, endothelial cells activate transcription factors and transcription cascades. One of these factors is Phorbol 12-myristate 13-acetate (PMA). This transcription factor is attached to the promoter of the t-PA gene and increases its expression. EET has fibrinolysis properties through the induction of t-PA and suggests that endothelial CYP2J2, a type of EET, may play an important role in vascular hemostasis (Koichi et al., 2001).

As previously mentioned, the body activates a coagulation system following any damages to the veins, and by using of platelets and coagulation factors forms a clot and thus prevents the bleeding of the vein. One of the important tasks of the coagulation system is hemostasis. In fact, when this system injured, activates the coagulation factor and causes clotting, and by activating anticoagulants such as anti-thrombin and proteins C and S prevents clot formation. The result of the plasmin activity on the fibrin is the production of small pieces under the general name of the FDP or products derived from the fibrin degradation, including D-Dimer. D-Dimer is not detectable in the normal state of the body, but in some cases, the D-Dimer measurements show an increase in the amount of this product and are clinically important. Therefore, the D-Dimer measurement test is one of the most important laboratory tests (Womack, 2003).

### 4. Responses and compatibility to practice in coagulation and fibrinolysis

Investigating on changes in coagulation due to practice suggests that the time of acute thromboplastin (APTT) after exercise is shortened. Of course, the role of gender and different training models should be considered. The effects of acute exercise on Prothrombin (PT) are unclear (Table 1). In both cases, shortened and unchanged PT was reported after acute training (Womack, 2003).

<table>
<thead>
<tr>
<th>Variable Coagulation</th>
<th>Chronic training compatibility</th>
<th>Acute training response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of active thromboplastin</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>Unchanged</td>
<td>Decrease/ Unchanged</td>
</tr>
<tr>
<td>Anti-thrombin time</td>
<td>Increase</td>
<td></td>
</tr>
<tr>
<td>Factor VIII</td>
<td>Decrease</td>
<td>Increase</td>
</tr>
<tr>
<td>Factor VII</td>
<td>Decrease/ Unchanged</td>
<td>Decrease/ Unchanged</td>
</tr>
<tr>
<td>Fibrin peptide A</td>
<td>Increase</td>
<td></td>
</tr>
<tr>
<td>Prothrombin fragments 1 + 2</td>
<td>Increase</td>
<td></td>
</tr>
<tr>
<td>Platelet activity</td>
<td>Increase</td>
<td></td>
</tr>
<tr>
<td>Platelet aggregation</td>
<td>Decrease</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Decrease/ Increase/ Unchanged</td>
<td>Decrease/ Increase/ Unchanged</td>
</tr>
<tr>
<td>PAI-1 activity</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
</tbody>
</table>

A significant increase in FVIII activity occurs after an acute exercise, and FVIII may stay up for a few hours in the recovery period. The increase in FVIII due to exercise and the FVIII antigen depend on the intensity of exercise, and it is not possible to increase in the sub-maximal activity and under lactate accumulation (LA). The von willebrand factor occurs almost at a 40 minutes training close to or above the threshold. The von willebrand factor increases in the maximum activity on treadmill, even above the lactate threshold. Therefore, moderate intensity exercises in sufficient time, increases the coagulation potential. However, TAT, pro-thrombin I and II, and fibrin peptide A rise after intensive exercise. Acute exercise does not have any effect on FVIII. Therefore, no change in FVIII Ag / FVIII c and plasma accumulation in exercise occur until fatigue. Of course, a slight decrease in FVIII c may be observed. An increase in FVIII in the exercise happens as a result of beta-adrenergic obstruction. Thus, the increase in von willebrand factor and FVIII can be the reason of coagulation in acute exercises. While most coagulation factors increase as a result of acute exercise, the effect of acute training on fibrinogen is not possible, but exercise with varied and moderate intensity increases significantly. Differences of individual and experimental methods may be responsible for these heterogeneous results. Of course, genetic cases should be considered in differences. The polymorphism genes, beta-fibrinogen and fibrinogen, affect the acute plasma in response to exercise. Cross-sectional studies show that APTT and PT are not affected by exercise.
during rest and immediately after exercise (Womack, 2003). A research showed that 12-week aerobic training results in decreasing of APTT in healthy inactive individuals with aged 20-60 years (Womack, 2003). FVII may be reduced following chronic aerobic exercise. FVII decreases among inactive men after 3 months of exercise is reported. Cross-sectional studies showed an inverse relationship between physical activity and fibrinogen (Womack, 2003). Increasing plasma fibrinogen may be due to an increasing trend of inflammatory factors such as C-reactive protein that increases after exercise. Fibrinogen significantly decreases after 3 and 6 months of aerobic activity. Fibrinogen was decreased after 9 weeks of aerobic and endurance training with moderate intensity. Fibrinogen activity in women with aged 60-80 years reduced after 9 months exercise. Fibrinogen increase is due to increasing of inflammatory factors such as C-reactive protein that increases after exercise (Womack, 2003). 

Acute exercise usually results in an increase in t-PA antigen and a decrease in PAI1. The magnitude of these responses depends strongly on the duration of the exercise and it is related to the state and form of exercise. Fibrinolysis activity increases with initial activity and release of t-PA. The release of t-PA from endothelial cells can occur as a result of hypoxia, arginine, vasopressin, epinephrine and increased thrombin. Increasing in fibrinolysis usually does not occur at intensity below 50% of maximum heart rate, because epinephrine increases at levels close to the lactate threshold. The exercise period may affect fibrinolysis responses to exercise, although the importance of exercise intensity is greater. The response to the training in moderate intensity occurs for 1 hour. In the marathon there is a very high increase in fibrinolysis. Moderate intensity and short duration (20 minutes) resulted in more severity fibrinolysis response. Therefore, the effect of exercise intensity on fibrinolysis is much more important than the duration of exercise. Unless much time is spent on training (marathon and cross country running) (Womack, 2003).

Due to the effect of intensity, t-PA and PAI1 are related to VO2max. Improving aerobic capacity is important in fibrinolysis potential. Physical activity related to leisure time and work or occupation is not sufficiently adequate for fibrinolysis changes. Physical activity with high intensity in comparison with low intensity causes a more obvious decrease in PAI1. Of course, the effect of age should not be forgotten. Significant changes in fibrinolysis profile with exercise in elderly (60-82 y) were observed in comparison with young people (24-30 y). Fibrinolysis responses are significant in maximal exercises than sub maximal exercises. TPA increases after maximal exercise, which can be observed by clot degradation in the vein. PAI1 increases in sedentary and inactive people. TPA distinctions in sub-maximal and maximal exercises also in the fibrinolysis process are evident. But these distinctions may be largely due to differences in fibrinolysis resting profiles. Changes in coagulation and fibrinolysis potential are affected by ischemia (Womack, 2003). Coagulation and fibrinolysis variables have independent effects on cardiovascular patients, but they are also related and are reliable risk factors (Table 2).

As a result of practicing, coagulation and fibrinolysis responses in patients and inactive people is more perceptible than athlete and practitioner. Changes coagulation factors due to the practice may occur several hours after the training session. Regular aerobic exercises lead to improved fibrinolysis profiles and reduced coagulation potential in healthy and sick individuals (Womack, 2003).

**Table 2: Hemostasis variables in CVD patients compared to non-CVD individuals.**

<table>
<thead>
<tr>
<th>variable</th>
<th>Practice response</th>
<th>rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAT</td>
<td>increase</td>
<td>increase</td>
</tr>
<tr>
<td>VIII</td>
<td>increase</td>
<td></td>
</tr>
<tr>
<td>Von Willebrand Factor</td>
<td>increase</td>
<td>increase</td>
</tr>
<tr>
<td>Factor VII</td>
<td>increase</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>increase</td>
<td></td>
</tr>
<tr>
<td>activity t-PA</td>
<td>increase/unchanged</td>
<td>decrease</td>
</tr>
<tr>
<td>antigen t-PA</td>
<td>unchanged</td>
<td>increase</td>
</tr>
<tr>
<td>activity PAI1</td>
<td>unchanged</td>
<td>increase</td>
</tr>
</tbody>
</table>

**5. Response to the inflammatory processes due to exercise**

Inactive lifestyle is a risk factor and a powerful predictor for chronic diseases and early deaths. Low-grade inflammation has been proven to be a key factor in the pathogenesis of cardiovascular disease. Inflammatory processes also include maintaining the balance between coagulation and fibrinolysis. This shows a linear inverse relationship with the mortality rate due to the disequilibrium of the clot and its solubility. However, the desired effects of structural training programs and independent participation of physical activity on cardiovascular risk factors are still under investigation (Yu-Wen et al, 2014).

In response to intense training, interleukin 6 (IL-6) is secreted by the contraction of the skeletal muscle followed by a reactive release of CRP. Both factors of CRP and IL-6 can produce monocyte-tissue agent, platelet overactive stimulation, enhance the fibrinogen biosynthesis, and increase the formation of fine particles and erythrocyte. Therefore, it causes Prothrombotic release. In contrast, regular exercises and physical activity against all mortality factors provide a protective mode by promoting the production of pro-inflammatory cytokines, increasing anti-inflammatory modifiers and antioxidant development, and promoting fibrinolysis activity. Low-intensity exercises in the thrombosis play a beneficial role by reducing inflammatory processes and fibrinolysis factors (Yu-Wen et al, 2014).

Researchers (Acil et al., 2007) considered the central role of inflammatory and coagulation mechanisms in the development of atherosclerosis in healthy and inactive middle-aged men. In this study, the experimental group performed an aerobic exercise program at 75% to 85% of maximal heart rate, three days/week for three months. There was no significant difference in fibrinogen and fibrin d-dimer levels. Regarding the results of this study, has been shown that regular aerobic exercise in middle-aged men reduces inflammatory factors, which have a beneficial effect on heart health and reduce the risk of cardiovascular disease.
6. Hemostasis response to aerobic exercises

It seems that in healthy adults, resistance training causes a slight change in coagulation potential. The effect of long-term exercise on fibrinogen is ambiguous, but the findings of cross-sectional studies show a small amount of fibrinogen in the active individual compared to inactive individuals. And the findings from exercise studies show an increase, decrease or no change in fibrinogen levels after exercise. However, endurance training plays an important protective role in cardiac patients, while exercise has been shown to prolong the active thromboplastin time and reduce coagulation factor VIII activity and fibrinogen levels (Womack, 2003). Several researchers have reported greater activity of tissue plasminogen activator after short-term physical activity in the active individuals compared to inactive individuals (Speiser, 1998). These changes are associated with a greater release of plasminogen activator or a decrease in the production of plasminogen activator inhibitor complexes that has been reported in elite people with rest conditions (De Paz, 1992).

In the resting conditions, the activity of t-PA is lower and after exercise, it is still lower in elite individuals than sedentary individuals (Speiser, 1998). The production period of plasmin is much higher, subsequently, fibrin degradation is higher. De pas (1992) showed higher levels of fibrin and fibrinogen degradation products in elite runners compared to inactive ones. Most of the evidence and findings were shown the further increase in fibrinolysis after aerobic exercise. Any changes in the function of endothelial cells and hemostasis that have been discussed have important consequences for cardiovascular health. Healthy endothelial cells support anti-coagulant, anti-thrombotic and anti-inflammatory conditions that are protective against atherosclerosis and coronary artery disease. Nitric oxide and prostacyclin, released from the endothelium, prevent the adhesion of the platelets and myosites to the vasculature. In addition, nitric oxide prevents the proliferation and migration of smooth muscle cells. It also prevents endothelin function as a venous dilator and smooth muscle proliferator (Gibbs et al., 2001).

Changes in hemostasis occur regards to the type, duration and intensity of the training. Researchers measured the values of pro-thrombin time (PT), active phase thromboplastin (aPTT), d-dimer, fibrinogen, plasminogen activator inhibitor (PAI-1) and thrombin activating fibrinolysis inhibitor (TAFI). PAI-1 values increased significantly after sub-maximal exercise and during the resting. TAFI values decreased significantly in minutes 15 and 60 compared to baseline and after exercise (minute zero). The activity of the fibrinolysis system is observed after acute submaximal aerobic exercise in healthy-sedentary participants (El-Sayed, 1996). (Francis, 2014), in their research showed that a decrease in fibrinolysis potential occurs with both age and physical activity and increases the risk of cardiovascular disease. Plasmin was activated by t-PA, while PAI-1 prevents its function. Both of these factors are expressed by human skeletal muscle (SM). Recently, no study has been conducted on changes in fibrinolysis -SM activity due to the age and aerobic exercise. The results of the study showed that high levels of aerobic fitness are associated with increasing fibrinolysis activity in SM.

Hemostasis response to short-term aerobic exercises

Short-term sports activities cause changes in the function of various blood components involved in coagulation and fibrinolysis, and enhance pre-coagulation and fibrinolysis conditions. In addition, plasma volume changes during exercise. The greatest reduction in plasma volume occurs in the first 5 to 10 minutes of physical activity (Smith, 2011).

Platelets

Aerobic exercise increases accumulation and platelet activity, and stimulates thrombosis in healthy and inactive people. Height intensity exercise can increase the potential of thrombosis; especially severe exercise causes ischemia events. Platelet activation because of the catecholamine increases during exercise. By increasing intensity of physical activity, the amount of catecholamine also increases. Norepinephrine reduces thrombosis by activating nitric oxide and prostacyclin⁶⁰. Inflammatory mediators cause monocytes and T lymphocytes to migrate to the intima of the vessels. Then the smooth muscle of the vein is injected into vascular endothelial cells, and vascular resistance increases by the LDL entry into the vascular wall and the endothelial wall of the vessel, and the vessel is prone to tearing. The rupture of the plaque of atherosclerosis and the formation of thrombosis is due to the development of an infarction (Smith, 2011).

Coagulation

Intense sport activities, moderate and long-term sport activities are essential for excessive coagulation and increasing fibrin formation in the body (El-Sayed, 1995). Blocking of beta-adrenoceptor and nitric oxide is linked to the disruption of increasing in the VIII coagulation factor. In the first few hours after intensive exercise, the coagulation potential remains at the highest level. The activity of thrombin-anti-thrombin complex of pro-thrombin 1 and 2, fibrinopeptide A, and coagulation factor VIII totally remains high, and the increase in 1 and 2 pro-thrombin units even continues. The values of thrombin-anti-thrombin complexes, pro-thrombin 1 and 2 fragments and fibrin peptide A return to baseline values 21 hours after exercise, but activated thromboplastin time is lower. In the early stages of recovery and during exercise the risk of acute coronary artery disease increases (Rajni & Kaul, 2003).

Fibrinolysis

During and after very intense exercise, moderate and prolonged, t-PA antigen and the plasmin-anti-plasmin complex increase, which showed the rise of plasmin formation. This situation accelerates the increase of fibrin decomposition products. It is likely that the lack of increased fibrin degradation products during moderate exercise indicates a significant increase in coagulation rather than limitation in fibrinolysis. If moderate-intensity exercise is not the main stimulant of coagulation, and a little fibrin is formed with this kind of activity, fewer fibrins will be available. The greatest increase in fibrinolysis will be observed immediately after intensive exercise. However, fibrinolysis indices such as t-PA and plasmin-anti-plasmin complexes remain high in hours after exercise. Evidence suggests that short-term aerobic exercise increases coagulation and fibrinolysis, but exercise in healthy people stimulates fibrinolysis more than coagulation. This is not true for cardiovascular patients who already have a higher coagulation and fibrinolysis rate in resting conditions compared to healthy people of the same age. Evidence and studies show that patients with cardiovascular disease also have an increased coagulation due to exercise rather than healthy people. After short-term exercise, fibrinolysis is recovered at a higher rate. Coagulation increases cardiovascular events during the period of short-term aerobic exercise activity. Acil and colleagues⁶ observed a delay in coagulation recovery after exercise in cardiac patients compared with healthy subjects. Obviously, hemostasis changes after short-term aerobic exercise lead to dangerous events,
especially for heart patients. Posthuma and colleagues in their research said that events such as venous thromboembolism and myocardial infarction are associated with exercise. These events are specific to the Prothrombin state in which interactions between coagulation factors, capillary walls, and fibrinolysis systems play an important role. The duration and intensity of exercise have different effects on hemostasis, and especially high intensity exercises increase the risk of thrombotic problems. However, the mechanism of these events is still unclear and there is an ambiguity. Generally, the hemostatic profile is mainly influenced by the intensity of the exercise, and this is more tangible when comparing the intensity of the exercise above 80% with intensity of less than 60% (as the platelet and clot increased). According to finding the events of the thrombotic are due to high training intensity (Posthuma, 2015).

**Maximal and sub-maximal exercise effects on thrombosis**

Studies show that people who do aerobic exercises are less likely to develop cardiovascular disease and have a longer life span. However, there is a paradox that people who is exposed to short-term and acute aerobic exercises are more likely to develop CVD. Although those who do aerobic activity are much less likely to have CVD than inactive people. Current research and studies have shown that chronic and prolonged aerobic exercises have different benefits than acute exercises. Individuals that do chronic exercises may have to benefit in term of thrombosis through fibrinolysis and coagulation (Thrall et al, 2007).

**Thrombotic response to maximal exercises**

Patients with CVD and non-patients compared with the control group showed increased platelet activity, coagulation and fibrinolysis as a result of maximum exercise (Bartsch, 1995 & Gibbs, 2001). It seems that fibrinolysis and coagulation are in parallel, and imbalance between them causes thrombosis. Studies have shown that there is a window of vital importance for cardiovascular patients, which usually lasts about 2 hours. All coagulation events in patients with cardiac arrhythmias occur during recovery and it has been shown that patients have a potential clotting during this recovery period. The researchers concluded that maximal exercise caused platelet aggregation and platelets also produced reactive oxygen species (ROS). But if warm-up is done, the platelets are suppressed (without the production of ROS) (Petidis, 2008). In contrast, light aerobic exercise suppresses platelet masses and inhibits the production of ROS (Kobusiak et al, 2006).

**Thrombotic response to the submaximal exercises**

The researchers believe that the sub-maximal exercises activate fibrinogen, coagulation and platelet activity. 45 minutes of exercise with intensity 70-65% of maximum heart rate increased fibrinolysis (increase in PAP) increased coagulation (decrease in thromboplastin time and increase in factor VIII), increased platelet activity (increase in platelet count) and increased in function of Endothelial (increase in von Willebrand factor [VWF]). 30 minute of sub-maximal aerobic exercise increases fibrinogen, t-PA antigen and PAI1 reduction in 25-year-old healthy and patient women (with a maximum of 50 watts). The researchers showed that 60 minutes of submaximal aerobic exercises with intensity of 80-75% VO2 in 21 young women with 22 years of age increase F1 + 2, TAT, FPA and D-dimer. Generally, researchers consider the intensity of exercise to be very effective in fibrinogen activity and coagulation. The researchers concluded that sub-maximal aerobic exercise did not change the factor 4 platelets and thromboglobulin beta, and only increased vWF (patients with arterial fibrillation). This is while maximal exercises increase all of the above factors (Selda et al., 2010). (Selda et al., 2010) in their research have shown that the different benefits of chronic submaximal-aerobic exercises than acute maximal aerobic exercises may be due to their effects on thrombosis. Most of the findings come from healthy people, which may be due to changes in platelet function, coagulation and fibrinolysis. However, acute exercise has a greater relationship and chronic exercise has greater benefits in the patient population. These patients may take medications that affect the pathway of thrombosis. In researches, the use of medication, the number of patients, the intensity of exercise and the components of the exercise, including the important effect of warming up, and the order of the exercise should be considered (Neuman et al., 2013). Many researchers (Gholami, 2012 & Petidis, 2008) have investigated the relationship between physical activity and serum t-PA in women and men, some studies have shown that physical activity improves fibrinolysis function. Most researchers (Hegde, 2001) have admitted that physical activity release t-PA from endothelial cells and stimulates fibrinolysis system. This process will not increase in any activity unless the intensity of the activity exceeds 50% of the maximum heart rate. Therefore, it can be said that the activity of the fibrinolysis system depends on intensity of physical activity (Hegde, 2001). The research conducted by (Rängemark et al, 1995) showed that cardiovascular hemostasis is affected by exercise intensity. 4-minute exercises on the ergometer cycling increased the t-PA rate in comparison with the control group. In another study, the effect of training intensity on cardio respiratory preparedness and risk factors for coronary artery disease was studied. VO2max, lipid, lipoprotein and fibrinogen in 64 sedentary males, was investigated in moderate intensity exercises (three sessions, 400 kcal in week with 60% VO2max) and high intensity exercise (three sessions of 400 kcal in week with 80% VO2max). The results showed that high intensity of exercises are more effective in improving cardio respiration, lipid reduction (Tofifghi et al, 2012) and fibrinogen reduction (Donovan et al., 2005). Some studies have shown that exercises using different protocols do not have a significant effect on serum t-PA levels (Bobadilla et al, 1993) and some others have shown a decrease (Hegde, 2001). Therefore, it can be said that the impact of different activities on fibrinolysis indicators is different (Gholami, 2012).

In a research, (Khodadadi & Atabak, 2005) examined the acute responses of plasma fibrinolysis system to submaximal aerobic activity in active and inactive people. One submaximal exercise activity with 70% of maximal oxygen consumption was performed on the ergometer cycling for 30 minutes. Blood samples were collected for measuring the activity of t-PA and PAI1 at rest, immediately after activity and after 30 minutes of recovery. The activity of t-PA following exercise was significantly increased in both trained and untrained groups, but returned to baseline after the recovery period. The t-PA activity in the immediately after exercise and also after the recovery period in the trained group was significantly higher than the UN training group. PAI1 activity did not change due to exercise, and there was no significant difference between the two groups. The findings indicate that high physical fitness plays an important role in the responses of the fibrinolysis system to exercise activities. It seems that higher fibrinolysis activity in active subjects in response to stress such as exercise is the adaptation that achieved through regular exercise and can be considered as an important mechanism for confronting with cardiovascular events (Khodadadi & Atabak, 2005).

(Khodadadi & Atabak, 2005) compared the fibrinolysis responses of athletes to submaximal exercise at different times of the day. Two sessions of
submaximal exercise activity with 70% maximal oxygen consumption (VO2max) were performed on an ergometer cycling for 30 minutes in the morning and evening. The t-PA activity increased in both sessions after exercise. After returning to the initial state, it returns to the base values. PAI1 activity did not change due to exercise. But its activity in the morning was significantly higher than the evening. The results of this study showed that exercise activates the fibrinolysis system. However, this increase returned rapidly to the initial state. In addition, day time plays an important role in the development of fibrinolysis due to exercise activity.

(Jahangard, 2005) investigated the acute and enduring effects of short-term aerobic exercise on coagulation factors, fibrinolysis, and lipid patterns in menopausal women. 5-minute warm up, 25-minute aerobic exercise, 5-minute active recovery and 15-minute non-active recovery in the experimental group was performed. The results of this study showed that short-term aerobic exercise intensified the acute response of the fibrinolysis system and significantly decreased the acute and sustained activity of the coagulation system in healthy postmenopausal women. It seems that regular and continuous sub-maximal aerobic exercises result in sustained reduction in coagulation activity.

(Rezaeiyan, 2006) examined the effect of regular aerobic exercises on the activity of coagulation factors in healthy young men. Individuals trained 3 times /week for 8 weeks, each time for half an hour with a ergometer cycling, that training program included 10-minute warm up, 15-minute aerobic exercise, and 8-minute cool down. The results showed that aerobic training for 8 weeks enhanced the response of Factor 9, 8, 7, von Willebrand, factor VIII and anti thrombin complex (TAT). However, the effect of these changes on the formation and degradation of thrombosis is not change due to exercise. But its activity in the morning was significantly higher than aerobic exercise. The present study suggests that addressing aerobic and resistance activities to counter the complications of the hemostasis and aging process is very useful.

7. Hemostasis responses to resistance exercises

The hemostasis system gives short-term response to resistance exercise. There are few studies on fibrinolysis responses to resistance exercises. Heavy resistance results in the release of plasma from the vessel to the outside of it and the volume of plasma decreases, but the volume of blood returns to the initial state after 30 minutes. Changes in platelets are also due to decreased plasma volume and increased catecholamine in resistance exercise (Smith, 2011). The researchers reported that several coagulation factors change after exercise. It is believed that factor VIII is a coagulation variable responsible for coagulation after exercise. The exercise activity increases factor VIII, which has a positive correlation with the weight. It seems that this increasing is related to the beta-adrenergic receptor pathway (El-Sayed 1995 and 1996). A study, reports increase in fibrinogen immediately after activity and returned to baseline values within 30 minutes. Researchers have suggested that the increase in fibrinogen is most likely due to concentration of the blood that is reversed during the recovery period when the plasma volume returns to normal. However, studies on fibrinogen changes in resistance exercises and related findings are less than aerobic exercises (El-Sayed 1995 and 1996). During resistance exercise, fibrinolysis is stimulated by the release of tissue plasminogen activator from vascular endothelium. T-PA is responsible of the formation of plasmin, which breaks the thrombosis and prevents excessive clotting. The t-PA increases after each type of exercise protocol including the resistance type, which response is dependent to intensity. In addition to increasing t-PA, the simultaneous reduction of PAI after resistance activity has been reported. PAI1 inhibits the formation of plasmin, therefore reduces the breakdown of blood clots (El-Sayed 1995 and 1996).Resistance training course can be effective in reducing body fat percentage and decreasing PAI-1 plasma concentrations in elderly women. Resistance training, three sessions per week at a severity of 42 to 65% of HRmax, has a significant effect on the reduction of plasma PAI-1 in elderly women (Li-Saw et al, 2001).

Researchers (Smith, 2011) demonstrated compared with untrained people (UT), resistance exercises (RT) have a lower capacity in the form of clot. As active thromboplastin (aPTT), lower PAI-1 before exercise and 120 minutes after exercise, show higher t-PA after exercise. There was no significant difference between the untrained and trained subjects for fibrinogen, Prothrombin 1 + 2 (PTF 1 + 2) and thrombin-anti thrombin complex (TAT). Physical activity in general and resistance training, in particular, alter the hemostasis variables such as platelets, coagulation variables, and fibrinolysis factors. However, the effect of these changes on the formation and degradation of thrombosis is not fully understood. In addition, responses depend on the used exercise protocols and the studied population.

8. Effect of concurrent (resistance-aerobic) exercises on coagulation and fibrinolysis factors

There is contradictory information about the effect of concurrent exercise (resistance-aerobic) on coagulation and fibrinolysis factors (Tofighe et al. 2014). (Mirsaeidi, 2012) examined the effect of 8-week concurrent (resistance-aerobic) training on coagulation and fibrinolysis factors in elderly men. The experimental group participated in a concurrent exercise program (3 days /week, for 8 weeks). After 8-week concurrent training, fibrinogen levels and platelet value decreased significantly in the experimental group compared to the control group, and PT, PTT and d-dimer fibrinolysis factor simultaneously increased. Concurrent activities can be useful in countering the threatening complications of hemostasis and the aging process, and should be used as an appropriate exercise protocol for maintaining health in these individuals. It is suggested that new and different practice protocols, especially in the elderly and vulnerable, should be considered (Mirsaeidi, 2012). (Sobhani et al.,2016) examined the long-term effects of high intensity and concurrent interval exercises on coagulation and fibrinolysis parameters in non-athletic young healthy men. The exercises were performed for 8 weeks, 3 times /week, in two groups of high intensity interval and concurrent. 8 weeks high intensity exercise and concurrent exercise reduces coagulation progression and increases fibrinolysis activity. Aerobic exercise reduces the number of platelets and reduces platelet mass and also reduces cardiovascular
disease. In the present study, 8-week concurrent training reduced blood fibrinogen levels, while high intensity interval exercises did not affect fibrinogen levels. Researchers have reported a reduction in blood fibrinogen levels after aerobic training, because of a decrease in fat percentage, body weight, body mass index, and suggested that they are directly related to fibrinogen concentration in the blood. Fibrinogen reducing is also attributed to reduced fat and body weight in resistance exercises (Tofighee et al.2014), maybe reducing the activity of cytokines in concurrent exercises reduces the concentration of fibrinogen in the blood or reduction of fibrinogen synthesis in the liver is the adaptation of the musculoskeletal system (Shehab et al. 2017). The activity of cytokines, including interleukin-1, is reduced. Inter-lucin-1 response decreases with increasing physical fitness, which is effective in reducing the synthesis of fibrinogen in the liver (Tofighee, 2012, 2014 and 2015). The main cause of cardiovascular disease in young people with our traditional risk factors (such as increased fat, high blood pressure and diabetes), increasing in clot formation and thrombosis. Considering the importance of resistance training in individuals' physical abilities, (Habibi et al, 2010), studied the effects of combined aerobic-resistance and aerobic training on coagulation activity in healthy young men. The aerobic group subjects participated in a 24-minute moderate program on an ergometer cycling. In the concurrent group, 12-minute resistance training with a 60% intensity of 1 RM max (5-first session) and 80% intensity IRM (5-second session), immediately after that, they pedaling 12 minutes on an ergometer cycling. 10 sessions of exercise significantly decreased PT in the aerobic and fibrinogen groups in both aerobic and concurrent groups, while PTT in both aerobic and combination groups increased significantly. It seems that performing 10 sessions of aerobic-resistance exercise and aerobic with moderate intensity can reduce coagulation activity.

Researches showed (Tofighee et al. 2014 and 2015) that concurrent exercises, in contrast to endurance and strength exercises, will improve the body composition and cardiovascular health. Weight was decreased in the endurance group. Also, there was a significant increase in IRM of the half-squat movements and chest compression in the resistance and concurrent training groups. None of the 3 types of exercises made changes in serum TNF-α level. Concentration of testosterone did not change in any training groups, but cortisol in the resistance group increased significantly, and the lipoprotein profile improved in all three groups. Resistance training increased the pre-inflammatory cytokine levels of TNF-α and cortisol hormone, which can be related to the training load of this group. It seems that the combination of endurance and resistance training has neutralized the effects of these two types of exercises. Also, concurrent training can be used to modify the lipid profiles.

(Zamanpour et al., 2017) studied the effect of fast and concurrent (aerobic-strength) exercise on some inflammatory markers and insulin resistance in women with type 2 diabetes mellitus (T2DM). Regular exercise has anti-inflammatory effects and suppresses systemic inflammation. The results of this study showed that there was no significant difference between the effect of speed and concurrent training on factors such as TNF-α, IL-6, hs-CRP and glucose. But in the case of insulin and insulin resistance, the difference between groups was significant. It seems that, given the greater impact of speed training on some inflammatory factors, speed training compared to strength-endurance exercises can have better anti-inflammatory conditions for women with type 2 diabetic.

9. Discussion

Cardiovascular homeostasis and its regulation is complex, with different pathways and mechanisms involved, each of them may be potentially controlled by various regulatory factors. Disturbance of blood hemostasis is recognized not only as a coronary risk factor, but also as a risk predictor of cardiovascular disease. Maintaining the blood hemostasis plays an important role in the survival of human beings in advanced world that causes inactivity, obesity and other cardiovascular risk factors. The stability and balance of the main coagulation and fibrinolysis factors have an important role in maintaining homeostasis. Aerobic, Resistance and Concurrent exercises play a significant role in modulating the main coagulation and fibrinolysis factors.

Cardiovascular diseases such as angina pectoris, infarction, atherosclerosis and stroke are the most important and greatest cause of death in the world. Fibrinolysis and coagulation are in parallel, and imbalance between them leads to thrombosis. Every change in coagulation - fibrinolysis factors depends on the type, intensity and duration of exercise. Several events that occur before, during and after the exercise can influence coagulation and fibrinolysis. Before essential performance, if warm up is don, the platelets return to the base, but without warm up, they remain at the same level and cause thrombosis. Warm up increases the temperature of the blood and increases the tension and mobility of the molecules, particles and parameters and prevents the platelets from depositing. In other hand, thromboxane B2 proved to be the most significant serum parameter related to platelet activation and the consequently increased risk of incipient clotting. Warm up is associated with a reduction in shed blood thromboxane B2. Some coagulation factors increase at high levels, close to the lactate threshold and they are sensitive to acute and severe exercises. Severe interval exercises have different effects on coagulation and fibrinolysis factors and usually reduce PAI1. In Fibrinolysis factors, intensity is also very important. The effect of the maximal and chronic exercises on coagulation factors reduces these factors. Most fibrinolysis factors are susceptible to chronic submaximal exercises with duration of over 1 hour. Therefore, the effect of intensity and duration on fibrinolysis is important. Fibrinolysis does not occur at intensity below 50% of maximum heart rate. Therefore, the role of intensity is greater than the duration unless the duration of the exercise be high (over one hour) such as Marathon and Cross country running and other long-term sub-maximal activities. Therefore, there is a direct and high correlation between coagulation and fibrinolysis factors with VO2max. 60 min sub-maximal aerobic exercise with intensity of 80-75 increases proteins of plasmaj (t-PA and PAI1), Plasminogen, FDA, TAT, F1 + 2 and d-dimer, while maximal exercises increase the coagulation factors. Regular aerobic exercises increase the production of pro-inflammatory cytokines by modifying anti-inflammatory and anti-oxidant factors and promoting fibrinolysis. On the other hand, aerobic exercise by releasing nitric oxide and prostacyclin reduces the platelet adhesion, and nitric oxide prevents the migration of smooth muscle cells of the vessel. In these exercises, the plasmin is activated and the PAI decreased. High levels of physical fitness are associated with increased fibrinolysis. Activation of the platelet caused by the physical activity is achieved by increasing the amount of catecholamine during exercise. Aerobic exercises and subsequently weight loss improves inflammatory parameters. Weight loss due to aerobic exercises can control oxidative stress, platelet activity and chronic inflammation. 10% of weight loss during aerobic activity can control and correct platelet arrhythmias. Aerobic exercises with decreasing weight, increases t-PA antigen and t-PA activity, and reduces the antigen and activity of PAI1. Increased PAI1 is associated with high BMI. Six months resistance activity reduces fibrinogen and PAI1 and increases t-PA. Vonwillebrand factor and t-PA antigen was decreased during two VO2max tests. In general, it can be concluded that the
effect of aerobic activity on coagulation and fibrinolysis factors has a significant effect when associated with weight loss, so that weight loss reduces inflammatory cytokines and increases the anti-inflammatory cytokines in obese men or women. One of the most important events in obese people is the impairment of the PFK activity. Aerobic exercises improve the function of this enzyme and improve the glycolic sis process. When intensity of aerobic activity increases, the amount of catecholamine also increases. Norepinephrine reduces thrombosis by activating nitric oxide and prostacyclin. Maximal aerobic exercise is essential for the formation of fibrin in the body. At the initiation of intense aerobic exercise, the potential of coagulation and the activity of the anti-thrombin-thrombin activity are at the highest level and returns to the baseline in 21 hours of recovery. All coagulation events occur in the recovery phase. As already mentioned, in response to intense exercise, interleukin 6 (IL-6) is secreted by the contraction of the skeletal muscle. IL-6 can produce monocyte-tissue agent, platelet overactive stimulation, enhance the fibrinogen biosynthesis, and increase the formation of fine particles and erythrocyte. Therefore, it causes prothrombin release. Prothrombin is one of the important factors in coagulation (Already mentioned). After high-intensity exercise, IL-6 can be produced locally. 10-15 min recovery with intensity 50%VO2max strategies could improve performance by minimizing cytokines such as IL-6. On the other hand, during and after intensive aerobic exercise, plasmin increases, this accelerates fibrin degradation. Decreasing this factor and the lack of fibrin degradation factors result in no significant increasing in coagulation, not limitation in fibrinolysis. Fibrinolysis indices remaining at high levels for several hours after physical activity. Short-term aerobic exercise affects fibrinolysis more than coagulation, but it is more likely in patients with coagulation (Khademi et al, 2019). Extreme resistance results in the release of plasma from the vessel and its volume reduction. Changes in platelets and epinephrine are the result of reduced plasma volume. Resistance exercises increase the amount of VIII associated with the beta-adrenal receptor pathway. Increasing fibrinogen is the result of concentration of the blood. Resistance exercises also release t-PA, and decreased PAI after resistance exercise. In short-term, but intense exercises such as resistance, the effect of resistance exercises on coagulation and fibrinolysis factors has been reported more than aerobic. Reducing in activity of cytokines, due to concurrent exercise, reduces fibrinogen concentration. In association with the reduction of fibrinogen synthesis in the liver, the adaptation of the musculoskeletal system should be considered that the activity of cytokines, including IL-1, is reduced. IL-1 response decreases with increasing physical fitness. This decreasing reduces the synthesis of fibrinogen in the liver cells. So far, comprehensive research has not been conducted on the major factors of fibrinolysis and coagulation. The research conducted with different training methods and scattered factors does not provide us with comprehensive information in this regard, and some of the information provided was contradictory. So doing different training protocols in parallel with each other and with varying intensity and duration of research is necessary. The knowledge about the changes in blood hemostasis in response to different modalities of physical training will definitely be essential in future research (Khademii et al, 2019).

10. Conclusion

- In order to achieve health aims, especially blood homeostats, discipline in exercising and observing the principles of exercise is essential.
- Daily and occupational activities and leisure time have no effect on fibrinolysis and coagulation factors.
- Fibrinolysis and coagulation are affected by the severity and duration of the exercise.
- Fibrinolysis factors are more affected by the duration of the exercise.
- Long-term aerobic exercises, more than 50% of HRmax (60 minutes or more than it) that result in weight loss, affect the fibrinolysis factors.
- Resistance (More than a third of 1Rmax) and severe exercises (more than 85% of maximal heart rate) have a significant effect on coagulation factors.
- Concurrent exercises have a significant effect on coagulation and fibrinolysis factors using aerobic and resistance exercises. Of course, its effects on fibrinolysis are more evident.

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