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Haemostatic activation in acute coronary syndrome patients in relation to physical exercise

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Backgound: Thrombosis is regarded to be a key factor in the development of acute coronary syndromes in patients with coronary artery disease (CAD), Platelets are known to play a fundamental role in acute coronary syndromes(ACS). After atherosclerotic plaque rupture, platelets can form pathogenic, occlusive thrombi leading to acute ischemic events. The precise mechanisms of platelet activation in acute coronary syndromes are still under investigation. Physical activity could regulate the development of ACS via effects on platelet function. Several studies have shown that acute physical exercise increases platelet reactivity, typically assessed by aggregation assays, in both healthy individuals and in patients with cardiovascular disease. The aim of this study was to investigated the effect of moderate and strenuous exercise on arterial thrombus formation.

Subjects and Methods: Assay of some hemostatic marker as Platelet activation , thrombin generation (TF(pg/ml),TAT_ µ g/l and dimerand tPA concentration) von Willebrand factor,platelet aggregation tests,_Coronary Angiography. haemostatic parameters in patients with ACS correlated with other clinical parameters under physical exercise **.**

Results: Patients with ACS showed higher values for fibrinogen , tPA , TAT_ , as indicators for a thrombin synthesis, and a marker for prothrombotic conditions, was elevated in patients with ACS,. Von Willebrand factor and D-dimer showed no statistical significant differences during rest., Exercise increased hemostatic parameters in an strenuous physical exercise in ACS Patients(< 0.05). Exercise also increased plasma levels of fibrinogen and von Willebrand factor ,but there was an increase in the generation of T-AT complexes,. ($P < 0.05$). Exercise did not affect platelet aggregation regardless of its intensity when triggered by the agonists ADP or collagen.

Conclusion: Strenuous but not moderate exercise increases the thrombotic tendency in healthy sedentary male volunteers

Keywords:

Activation, acute coronary syndromes, adhesion, aggregation, ant platelet agents, platelet, thrombosis.

Introduction

platelet activity plays a critical role in thrombus formation, which is central to acute coronary syndromes (ACS), including non-ST-segment elevation (NSTE)-ACS (comprising unstable angina pectoris and non-ST-segment elevation myocardial infarction [NSTEMI]) and ST-segment elevation myocardial infarction (STEMI), and has been implicated in poor clinical outcome(**Jax *et al*.,2009)** . Platelets not only impact coronary thrombus but are major contributors to microcirculatory dysfunction and vascular inflammation. Different mechanisms including endothelial dysfunction,platelet hyperactivity, and abnormalities in coagulation and fibrinolysis have been implicated for this increased atherothrombotic risk. Platelets play an important role in atherogenesis and its thrombotic complications in diabetic patients with acute coronarysyndrome (**Lee *et al*., 2012).** Efforts to inhibit platelet function, including antiplatelet therapy, are paramount to the management of ACS; thus, a growing recognition of the various pathways driving platelet activity has given rise to the need for multiple agents that impart complimentary mechanisms of action(**Jax *et al*.,2009)** physical activity could regulate the development of ACS via effects on platelet function (**Furie *et al*.,2008)**. Several studies have shown that acute physical exercise increases platelet reactivity, typically assessed by platlelets aggregation assays, in both healthy individuals and in patients with cardiovascular disease . (**Balducci *et al*., 2010)**. The effects of chronic exercise training and physical deconditioning on platelet function also have been studied.

(Wang *et al*., 1999) demonstrated that sustained periods of exercise training suppress platelet adhesion and aggregation in healthy sedentary men and women.(**Lippi *et al*., 2009)**. The studies showed that platelet adhesion and aggregation were enhanced by acute strenuous exercise.. Another study showed that acute, strenuous treadmill exercise unregulated platelet reactivity in healthy, sedentary individuals, but not in healthy individuals who were habitually physically active**.(Okada *et al*.,2010)**.

The beneficial effects of chronic physical exercise on platelet activation in hypertensive patients without known atherosclerosis was studied by(**Meirelles *et al*.,2009)** .Some studies have assessed the impact of different levels of physical activity on platelet reactivity. In healthy individuals, acute, moderate-intensity physical activity was found to exert less of a stimulatory effect or no significant effect on platelet function, compared with strenuous physical activity**. (Antoniades *et al*.,2010)** . Increased plasma catecholamine levels during exercise appear to play an important role in mediating the effects on platelet reactivity. Epinephrine activates platelets, though one study suggested that norepinephrine, rather than epinephrine, is the main determinant of exercise-induced upregulation of platelet reactivity Consistent with the role of catecholamines in platelet

activation during exercise, aspirin therapy, which inhibits thromboxane-induced platelet activation, does not inhibit the effect of acute exercise on platelet reactivity in patients with CAD (**Barr *et al*.,1988**.) However, one study found no linear correlation between plasma catecholamine concentrations and in vivo platelet activation in high-endurance athletes during acute exercise ,suggesting that factors other than catecholamines mediate the enhanced platelet reactivity observed during and immediately following physical exercise. Acute physical exercise does not alter platelet intracellular free calcium concentration, a determinant of platelet reactivity. Protein kinase C plays a key role in regulating platelet activation. Sustained physical activity was found to inhibit the decline in platelet protein kinase C activity that occurs with aging.

Acute strenuous physical exercise has been shown to increase the release of procoagulant microparticles from platelets and shear-induced thrombin generation. While acute physical exercise increases platelet reactivity, it also is associated with activation of pathways that reduce platelet activation, perhaps as a compensatory mechanism. For example, acute vigorous exercise promotes release of nitric oxide from platelets .In addition, thrombin-induced expression of GPIIb/IIIa by platelets decreases in response to acute physical exercise, while the inhibitory of effect of prostacyclin on platelets is potentiated by exercise (**Cadroy *et al*.,2002)**. After plaque rupture plasma von Willebrand factor (vWF) binds to collagen, and platelets adhere to immobilized vWF via GPIb-GPV-GPIX and integrin $\alpha_{IIb}\beta_3$ (GPIIb/IIIa. GPIIb/IIIa also binds fibrinogen, which drives platelet aggregation and thrombus growth (**Christiaens *et al*.,2002)**. Adenosine diphosphate (ADP) and thromboxane A_2 bind to specific receptors on platelets to amplify their aggregation after plaque rupture. Platelets express alpha-2 adrenergic receptors, which likely play an important role in mediating effects of physical exercise on platelet function.(**Dahabreh *et al*.,2011**)

Patients and methods

This study was conducted in internal medicine hospital, Division of Cardiology and the consecutive patients included 32 subjects (12 females and 20 males) diagnosed as acute coronary syndrome their aged between 52 and 69 years, who were scheduled for elective coronary angiography,. Unstable angina pectoris, acute myocardial infarction within the last six months before inclusion into the study, and prior coronary interventions were exclusion criteria. The study also included 25 healthy subjects (10 females and 15 males) as a control selected to match the study group in age and gender and not taking any medication within 7 days before sampling. All patients were divided into the following two groups: 1- group ACS patents' without physical exercise 2-group ACS patents' with physical exercise . All participants signed informed consent before testing. All patients and -control group were subjected to the following :

1st)Full clinical history. 2nd)Thorough clinical examination, Patients were considered to be Exclusion criteria were prior myocardial infarction (< 1 month before inclusion), (i) tumour disease,(ii) Peripheral arterial occlusive disease, patients with ejection fraction < 30%, (iii) Acute infections, chronic rheumatoid diseases, and chronic obstructive pulmonary disease and chronic liver and renal diseases. A progressive exercise test was performed on trained subjects at baseline and every 4 wkS., The order of the subsequent three sessions was randomized. They were a resting session, *2*) a moderate-exercise session in which the exercise was performed during 30 min at a constant workload, and *3*) an intense-exercise session in which the exercise was performed during 30 min at a constant workload. Blood collection for measurement of platelet aggregation, and other laboratory tests was performed immediately at the end of each session **>3rd)Laboratory investigations include** :

A-Routine laboratory investigations: Compelete blood picture(cell dyne 3500),lipograms (total cholesterol,HDL-C, LDL-C,TG) serum blood sugar(cobas integra 3.3.45), glycohemoglobin (HbA1c) (Variant 2, BioRad).

B-Specific investigations included:

Platelet activation and thrombin generation were determined by measuring plasma levels of thrombin-antithrombin complexes (T-AT), blood (4.5 ml) WAS collected in tubes containing a mixture (0.5 ml) of platelet inhibitors and (sodium citrate, citric acid, Stago). Blood samples were immediately centrifugated (4,300*g*, 19°C, 5 min). The supernatant was collected and centrifugated to eliminate remaining platelets (8,000 *g*, 19°C, 5 min). Aliquots of plasma were stored at −80°C until assayed. T-AT were measured by immunoenzymoassays (, Stago, and Enzygnost-T-AT, Behring, Marburg, Germany.(**Pelzer *et al* ., 1988**).

Measurements of tPA : Plasma levels of tPA antigen were measured by means of a commercial limmunoenzymatic method (Imulyse tPA kit; Biopool).**(Vassalli, *et al* ., 1991)**

Platelet aggregation tests, blood was collected into a citrated vacutainer (Becton Dickinson, Meylan, France) containing 0.5 ml of 0.105 M trisodium citrate for 4.5 ml of blood. Platelet-rich plasma was obtained after a centrifugation at 150 *g* for 15 min, and platelet-poor plasma was obtained after a second centrifugation at 1,500 *g* for 15 min. Platelet count was adjusted to 250 × 10^9/l by appropriate dilution of the platelet-rich plasma with autologous platelet-poor plasma. Platelet aggregation was performed with a platelet aggregometer (Helena Laboratories, Beaumont, TX). Agonists were ADP (2.5 and 5 μmol/l final concentrations, Stago) and equine collagen (1 and 5 μg/ml final concentrations, Nycomed). Arachidonic acid-induced platelet aggregation (1 mmol/l final concentration, BioData, Horsham, PA) was also performed to exclude subjects who had taken

aspirin. The maximum amplitude of platelet aggregation was measured and expressed as a percentage of the difference between platelet-rich plasma and platelet-poor plasma.

Von Willebrand factor plasma levels were measured immunologically by using the Laurell method (Assera-vWf, Stago). Fibrinogen plasma levels were measured by the method of von Clauss by the STA automate (Stago).(R validate a newly developed VWF collagen binding assay (VWF:CB) and VWF antigen enzyme-linked immunosorbent assay (ELISA) .

Coronary Angiography

In all patients coronary angiograms with imaging of the coronary arteries in different standardised projections were carried out. The degree of coronary artery stenosis was assessed by two experienced, independent examiners.

Statistical methods

Statistical analyses were performed using SPSS software (Statistical Package for Social Sciences for Windows; SPSS 15.0, Munich). For normally distributed parameters group comparison was made by use of paired and unpaired Student's t-test. Mann-Whitney U-Test was used for non-normally distributed parameters. . In comparing 3 groups, 1-way ANOVA for statistical significance, Were analyzed by the Mann-Whitney *U* test (2 groups). The Pearson correlation coefficient or the Spearman's rank correlation was used to describe the association between the variables in the study. A stepwise regression model was used to test the relationship of laboratory parameters on morphology. Chi square test was used for comparison of non-continuous data. Statistical significance was defined as p $P \leq 0.05$ Normally distributed data, presented as mean and ±SD.

Results.

Table1: Hematological parameters in ACS patients at rest and under moderate effect of physical exercise compared to normal control group .

	Controls N=25		ALL Patients (ACS) before Physical activity n =32		Test of significance
	Mean	**± SD**	**Mean**	**± SD**	**P value**
(pg/ml) TF	**392.7**	**111.6**	**645.3**	**242.7**	$P < 0.05$
TAT_ µ g/l	**11.9**	**4.8**	**22.8**	**7.3**	$P < 0.05$
D.dimer (ng mL)	**188.2**	**62.7**	**216.7**	**89.6**	p>0.05
Fibrongen (mg L)	**201**	**43**	**331**	**76**	$P < 0.05$
tPA, U/mL	130	**57**	**196**	**87**	$P < 0.05$
von Willebrand factor IU dL	**97.6**	**56.8**	**109.8**	**55.9**	p>0.05

Patients with ACS showed higher values for fibrinogen,TF ,tPA, , **TAT_** , as indicators for a thrombin synthesis and a marker for prothrombotic conditions, WERE elevated in patients with ACS, and statistically significantly. von Willebrand factor and D-dimer showed no statistical significant differences during rest.

Table2 :Hematologal parameters in ACS patients under Effect of strenuous physical exercise .

	Controls N=25		Patients (ACS) WithPhysical activity n =17		Patients (ACS) With0ut Physical activity n=15		Test of significance
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**p**
TF (pg/ml)	**287**	**68**	**295.97**	**42.7**	**1099.5**	**398.5**	$P < 0.05$
TAT_ µ g/l	**15.15**	**4.8**	**24.6**	**7.3**	**.466**	**64.**	$P < 0.05$
D.dimer	**167.2**	**62.7**	**316.7**	**89.6**	**694**	**271.9**	$P < 0.05$
Fibrongen m(g L)	**119**	**56**	**232**	**87**	**267**	**58**	$P < 0.05$
tPA U/mL	**123**	**64**	**133**	**78**	**186**	**43**	$P < 0.05$
von Willebrand factor IU dL)	**77.6**	**56.8**	**126.8**	**55.9**	**142.6**	**32.9**	$P < 0.05$

TAT: thrombin–antithrombin **TF: tissue factor**

The characteristics of exercise testing are shown in Table2. As expected, exercise increased hemostatic parameters in an **strenuous physical exercise in ACS Patients** ($P < 0.05$)Exercise also increased plasma levels of fibrinogen and von Willebrand factor ($P < 0.05$). AND the generation of T-AT complexes ($P < 0.05$)

(Table3) Effect of strenuous exercise on platelet aggregation and hemostatic plug formation in ACS patients. (Exercise did not affect platelet aggregation regardless of its intensity when triggered by the agonists ADP or collagen (Table3).)

Platelet aggregation %	**Controls N=25**		**Patients (ACS) With Physical activity n =17**		**Patients (ACS) Without Physical activity n=15**		**Test of significance**
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**P value**
2.5_µ_mol/lADP	**39.2**	**11.6**	**35.3**	**24.7**	**40.6**	**13.5**	> 0.05 **p**
5 µ_mol/l ADP	**56.9**	**28.8**	**60.5**	**32.9**	**68.9**	**23.7**	p>0.05
Platelet aggregation %							
1 µ_g/ml Collagen	**71.9**	**33**	**80.7**	**34.8**	**79**	**32.9**	p>0.05
5 µ_g/ml Collagen	**89**	**40**	**99.7**	**51.4**	**87**	**48.7**	p>0.05

(Table4) Correlation between platelets aggregation haemostatic parameters in patients with ACS .

Correlations of ACS patients with and without physical activity				
	(ACS) With PHYSICAL ACTIVITY (n=17)		(ACS) without PHYSICAL ACTIVITY (n=15)	
	r	p	r	p
Sex	o.15	0.56	0.41	0.02
Age	0.19	0.3	0.016	0.9
Waist-c	0.16	0.50	0.10	0.64
BMI	0.17	0.49	0.13	0.50
Smoking	0.05	0.83	-0.48	0.02
Systolic blood pressure	0.27	0.23	-0.59	0.004
Diastolic blood pressure	0.14	0.51	-0.19	0.40
Echo.	0.07	0.71	0.31	0.17
T. cholesterol	0.33	0.87	0.32	0.15
HDL cholesterol	0.05	0.8	0.01	0.97
Triglycerides	0.03	0.89	-0.52	0.26
LDL	0.26	0.24	-0.53	0.82
Total leucocytes count	0.14	0.53	-0.33	-0.14
Platelet count	0.04	0.93	-0.38	0.08
HBA1C	0.17	0.43	-0.05	0.86
TF	0.01	0.75	0.04	0.6
CRP	0.07	0.8	0.16	0.6
Hyperglycemia	0.02	0.57	0.05	0.84
D. dimer	0.01	0.81	0.62	0.44
TAT	0.31	0.63	0.13	0.02

Glycohemoglobin (HBA1C) • TF: **tissue factor** • total cholesterol • high density lipoproteins(HDL-C) • low density lipoproteins(LDL-c). •Waist circumference• body mass index (BMI) • echocardiogram (echo.) *TAT*: thrombin–antithrombin

Correlations of patients with ACS with or without With PHYSICAL ACTIVITY: we found, In group of patients with physical activity a strong positive correlation (smoking, ,total cholesterol, HDL-C, TG, platelets count, CRP and D.dimer). Mild positive correlation with sex, body mass index (BMI), Waist circumference, blood pressure, hyperglycemia and total leucocytic count. However, In group of patients without physical activity , showing strong positive correlation between CRP, age, waist, LDL, HDL and HBA1C, TF, hyperglycemia. With mild positive correlation with BMI and tissue factor

DISCUSSION

Acute physical activity increases the relative risk of ACS, although the absolute risk of ACS during or immediately after physical activity is low. Increased risk of ACS and coronary thrombosis during and immediately after physical exercise results from the enhancing effects of exercise on atherosclerotic plaque rupture, platelet reactivity, and blood coagulation. The risk of an adverse cardiovascular event during exercise is greatest in sedentary individuals with established coronary artery disease and other coronary risk factors, particularly hyperlipidemia. (**Hilberg *etal*.,2008)** ·. In contrast, sustained physical training reduces platelet reactivity and promotes changes in the blood coagulation and fibrinolytic systems that inhibit fibrin formation. However, sustained physical activity has not been established to reduce the risk of coronary plaque rupture or ACS.(**Gough *etal*.,2006)** ·

In our study ,Moderate levels of exercise or patients at rest did not significantly increase the thrombotic tendency). Previous studies have already shown that moderate exercise did not increase platelet adhesion and did not promote the release of platelet proteins or in vivo thrombin generation(**Ikarugi *etal*.,1999)** .In addition, as previously indicated, moderate exercise does not modify the density and affinity of platelets α_2-adrenergic receptors . Previous studies suggest that the increased thrombotic tendency seen after strenuous exercise may be related to the action of catecholamines. Exercise induces the release of cathecholamines. (**Goto *etal*.,1996**)At high concentrations, epinephrine promotes platelet aggregation, and at low concentrations, it potentiates platelet aggregation induced by other platelet agonists such as ADP or collagen. Thus, in flow conditions typical of atherosclerotic arteries, epinephrine has been found to enhance platelet deposition on severely damaged vessel wall and on collagen fibrils. In addition, acute exercise affects the characteristics of the platelet α_2-adrenergic receptor by which epinephrine interacts with platelets . This effect is intensity dependent ,whereas moderate exercise does not appear to

modify the density and affinity of these receptors, strenuous exercise increases their density on the platelet membrane surface but decreases their affinity for catecholamines. However, the increased thrombotic tendency observed during intense exercise probably includes other factors besides catecholamines.(**Hilberg *et al*.,2006)**

This increased thrombin generation in ACS under sever exercise, this is may be explain by (**Hilberg *etal*.,2008**) ,who reported that increased thrombin generation in ACS under sever exercise due to the tissue factor activity expression of circulating monocytes, which augments with exercise. It may contribute to the exercise-induced thrombotic tendency. However, the increase in thrombin generation, as measured by plasma levels of T-AT in our study,. Also, strenuous exercise had no significant effect on fibrin(.**Furie *et al*.,2008)**

The increased thrombotic tendency may also be related to the observed increased concentration of circulating blood cells and the coagulation factors fibrinogen and von Willebrand factor, but they also have been shown to persist despite correction for plasma volume changes.(**Degerstrom *et al*.,2006**) . Exercise-induced release of von Willebrand factor from endothelial Weibel-Paladegranules and a reduced clearance of hemostatic factors due to a diminished liver blood flow may also contribute to these findings.(**DeSouza *et al*.,1998**.) In contrast, the increased thrombotic tendency does not seem to be related to a change in platelet function per se (**Lee *et al*. 2012).** The susceptibility of platelets to aggregate in response to ADP and collagen did not change (**El-Sayed *et al*.,2007)** . Other studies examined the effect of exercise on platelet functions showed discordant results, but there were important methodological variations between these studies (.**Rivera *et al*.,2007)** .For example, platelet aggregation is dependent on the platelet count. Therefore, a standardized platelet count is an important parameter to take into account, especially because blood platelet count increases with exercise. Also, the type of exercise (running or bicycle) may influence platelet function(**Haskell *et al*.,2007)** .

Moderate levels of exercise did not significantly increase the thrombotic tendency Previous studies have already shown that moderate exercise did not increase platelet adhesion and did not promote the release of platelet proteins .In addition, as previously indicated, moderate exercise does not modify the density and affinity of platelets α_2-adrenergic receptors.(**Haskell *et al*.,2007).**

Conclusion

In conclusion, the present study shows that strenuous exercise increases the thrombotic tendency, whereas moderate exercise has no such effect. vigorous exercise does not present a high risk of thrombosis. However, for patients with coronary artery disease, strenuous exercise

may promote a plaque injury and facilitate the formation on this plaque of a platelet-rich thrombus. To minimize such a risk, our study suggests that people with coronary artery disease should train predominantly at moderate intensities and avoid heavy exertion. While much has been learned about the effects of physical activity on ACS and coronary thrombosis,. Furthermore, available research has focused more on the effects of exercise on surrogate markers (e.g., platelet reactivity in vitro, coagulation factor levels in plasma), than on clinically relevant endpoints, such as atherosclerotic plaque rupture, kinetics of thrombus formation, and the incidence of ACS**.**

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تخثر الدم فى مرضى متلازمة الشريان التاجي الحادة وعلاقته بممارسة الرياضة

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يعتبر تجلط الدم عاملا رئيسيا في حدوث متلازمات الشريان التاجي الحادة في المرضى الذين يعانون من مرض الشريان التاجى .

ومن المعروف أن الصفائح الدموية تلعب دورا أساسيا في متلازمات الشريان التاجي الحادة حيث وجد انه بعد تمزق اللويحة التى تحدث بسبب تصلب الشرايين، يمكن للصفائح الدموية ان تتلاصق فتكون جلطات تؤدى الى انسداد فى الاوعية الدموية فيقل الدم المغذى للاعضاء الحيوية ولكن لا تزال الآليات الدقيقة لدور تفعيل الصفائح الدموية قيد البحث.

وحيث ان تفعيل نشاط الصفائح الدموية وعلاقتة بممارسة الرياضة. مازال محل الدراسة. فالهدف من هذه الدراسة هومعرفة تاثير بين ممارسة الرياضه في مرضى متلازمة الشريان التاجى الحادةعلي تكوين الجلطات المبطنة لجدار الاوعية الدموية فى تفعيل الصفائح الموية والتهيئة لتكوين جلطات.

ويمكن الوصول الى الهدف من هذه الدراسة عن طريق فحص معملى لكل من:
درجة تفعيل الصفائح الدموية,الثرومبين , عامل فون ويلبراند,درجة تراكم الصفائح الدموية
بالاضافة الى تصوير الأوعية التاجية.ومن خلال هذة الدراسة وجدت علاقة وطيدة بين ممارسة الرياضه البسيطة و تفعيل نشاط الصفائح الدموية في مرضى متلازمة الشريان التاجى الحادة .

وجد ان ممارسة الرياضه الشديدة في مرضى متلازمة الشريان التاجى الحادةتؤدي الى ارتفاع مستوى عوامل التجلط ولكن لا يؤثر علي معدل التصاقات الصفائح الدموية.اما ممارسة الرياضة البسيطة فتؤدى الي ارتفاع بسيط في بعض العوامل مثل الثرومبين و الفبرونجين ذو دلالة احصائية اما ارتفاع عامل فون ويلبراندو دي د يمر فليس لهم دلالة احصائية.وكذلك اكتشفت هذة الدراسة ان ممارسة الرياضه البسطة والشديدة لا يؤثر علي معدل التصاقات الصفائح الدموية .

ولذلك توصي هذة الدراسة بممارسة الرياضة البسيطة في مرضى المتلازمة التاجية الحادة.