Effects of Cardiac Rehabilitation on Fibrinolysis in Patients with Coronary Artery Disease

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The aim of the present study was to demonstrate the influence of exercise component of a cardiac rehabilitation program on fibrinolysis in coronary artery disease (CAD) patients. Cardiac rehabilitation program was claimed to have an important role for improving quality of life and reducing the incidence of recurrent disease. The program used in the present study included aerobic exercise for 8 weeks, 4 days per week, 30 minutes per day at light to moderate intensity. Thirty-three male patients with CAD were recruited in the present study. Subjects from Thammasat University Hospital and King Chulalongkorn Memorial Hospital, whose age ranging from 40 to 70 years, were random assigned into 2 groups: control and experimental groups. The results showed that no significant differences in tissue plasminogen activator levels (t-PA) (both antigen and activity), plasminogen activator inhibitor-1 levels (PAI-1) (both antigen and activity) were observed in control and experimental groups after exercise training for 8 weeks as compared to the baseline. However, significant improvement of fibrinolysis via a decrease in PAI-1 activity level from 16.3(3.7) to 14.8(6.3) AU/ml ($p<0.024$) and an increase in t-PA activity from 2.3(0.8) to 2.7(0.5) IU/ml and t-PA antigen from 7.5(2.9) to 9.2(2.7) ng/ml ($p<0.01$) in experimental group were observed when compared between pre and post acute submaximum exercise (65%$VO_{2\ peak}$) at the end of the program. In addition the authors found a significant improvement in $VO_{2\ peak}$, resting heart rate, and serum triglyceride level in experimental group after 8 weeks of exercise training. This study demonstrated that patients with CAD participating in 8 weeks exercise cardiac rehabilitation program at light - moderate intensity could improve physical fitness and physical health although there was no significant change of fibrinolysis. The CAD patients should be advised to enroll in this cardiac rehabilitation program since it did not have any harmful effect due to the fibrinolytic function but it also augmented the patients' physical health.

Keywords: *Cardiac rehabilitation, Fibrinolysis, t-PA, PAI-1*

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Exercise training has assumed a major role in both the primary and secondary prevention of disease. It can prevent the illness as well as decrease the duration of illness. Studies have shown that exercise augments a positive effect on fibrinolytic system. Effects of exercise are increased fibrinolytic activities which are dependent on the exercise intensity and the duration. In coronary artery disease (CAD) patients, exercise training has presumed a major role in increasing physical performance, lifting the angina threshold in patients with symptomatic CAD, and improving myocardial perfusions.

Fibrinolysis is the mechanism involved in fibrin degradation through the proteolytic action of the serine protease plasmin [1]. This enzyme originates from the activation of proenzyme plasminogen by tissue plasminogen activator (t-PA). Tissue plaminogen activator is released into the circulation from the endothelium and rapidly inactivated by the endothelial type plasminogen activator inhibitor (PAI-1).

Impaired fibrinolysis may result from either low t-PA or elevated PAI-1 levels. It plays an important role in the development of CAD, and it is related to

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long-term mortality [2, 3]. Tissue plasminogen activator antigen levels in human plasma at rest range between 3.4 $\pm$ 0.8 ng/ml and 6.6 $\pm$ 2.9 ng/ml. This level increases about three folds by exhaustive physical exercise [4]. In healthy individuals, highly variable plasma levels of both plasminogen activator inhibitor-1 (PAI-1) activity and antigen were observed. PAI-1 activity ranges between 0.5 and 47 IU/ml. PAI-1 antigen in plasma ranges between 6 to 85 ng/ml [5] PAI-1 binds rapidly to t-PA forming a stable complex with a 1:1 ratio [6]. The active form of PAI-1 is unstable, with a half-life of 30 minutes [7].

Prospective and case-control studies have indicated that many of the proteins involved in coagulation and fibrinolysis that might contribute to a thrombotic tendency are related to the development of CAD. The suppression of fibrinolysis was due to high plasma concentrations of PAI-1 and increased plasma concentrations of factor VII, fibrinogen, and von Willebrand factor which are associated with the development of myocardial infarction [8]

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. Accumulating evidence indicates that exercise might favorably modify several of conventional CAD risk factors including blood lipid, obesity, blood pressure and insulin levels [9].

It is generally accepted that physical exercise enhances the fibrinolytic activity and induces changes in some hemostatic parameters. An increase in t-PA activity and decrease in PAI-1 levels have been described in healthy subjects following long-term exercise training [10-11]. It has been suggested that exercise could favorably influence the clinical course of patients with CAD through a reduction of PAI-1 levels [12].

Material and Method

The study protocol was approved by the local ethics committee, Faculty of Medicine, Chulalongkorn University. Before entering the program, all subjects gave written informed consent to participate in the present study. They were coronary artery disease patients treated at King Chulalongkorn Memorial Hospital and Thammasat University Hospital. The present study comprised of two groups of patients with coronary artery disease who were enrolled in a randomized trial, namely exercise group (n= 18, age 58 (7.0) years), and control group (n= 15, age 58 (8.5) years).

Body weight and height of subjects were measured by using a weight balance scale (Yamato, DP6100GP, Japan), and a wall mounted height-measuring board. The body mass index (BMI) was calculated according to the formula, body mass (kg)/height (m^2). The peak oxygen consumption (VO_{2peak}) of each subject was measured during the incremental exercise test using oxygen and carbon dioxide gas analyzer (Quinton Metabolic Cart, QMC, USA). Oxygen consumption (VO_2), carbon dioxide production (VCO_2), minute ventilation (VE), and other derived parameters were continuously monitored breath – by - breath using a computerized system (Quinton Metabolic Cart, QMC, USA). Data on VO_2 and VCO_2 were expressed in a standard condition of standard temperature pressure dry (STPD) and VE in the condition of body temperature pressure saturated with water vapor (BTPS). The Naughton protocol for treadmill was used in this exercise test. Intensity of exercise training used in the present study was 50%VO_{2peak} in the first week and 65%VO_{2peak} in the following weeks. During training, the authors monitored heart rate, recorded blood pressure before and after training session, evaluated RPE. The training was 8 weeks long, 4 days per week, 30 min per session with 10 min warm up and 10 min. cool down.

Blood Sampling and Preparation

To avoid the diurnal variation in coagulation and fibrinolytic variables, all blood samples were collected between 7:30 a.m. and 10:30 a.m. after a 12-hour overnight fast [13]. All phlebotomies were performed with minimal venostasis. The first 4-5 ml of blood was used for the study of lipid profile. Blood for determination of t-PA antigen, t-PA activity, PAI-1 antigen, PAI-1 activity, was collected in sodium citrate tubes.

Blood sampling for t-PA activity

It is extremely important to follow the acidification and centrifugation steps exactly as described below in order to minimize the in vitro inhibition of t-PA by PAI-1. Blood (9 volumes) was mixed with 0.1 mol/l sodium citrate (1 volume). One ml of this mixture was immediately acidified with 1 ml (1:1) acetate buffer working solution (2-8∞C) and centrifuged within 2 min at 3000 rpm for 20 minutes. The plasma was separated from the cells as soon as possible and then added 10 ml of 1 mol/l HCl to each 150 µl of acetate treated plasma.

The samples were kept at – 80 ∞C until used. Tissue plasminogen activity was analzyed using the reagent kit of t-PA activity assay (COASET[a] t-PA) (product of Chromogenix (Italy)).

Blood sampling for other fibrinolytic parameters such as t-PA antigen, PAI-1 activity, PAI-1 antigen was prepared as follows. Blood (9 volumes) was mixed with 0.1 mol/l sodium citrate (1 volume) and centrifuged at 3000 rpm for 20 minutes. The separated plasma samples were kept at – 80 ºC until used. The measurement of t-PA antigen, PAI-1 activity, PAI-1 antigen was done using the commercial reagent kits from Chromogenix (Italy) as follows: COALIZA[a] t-PA for t-PA antigen assay, COALIZA[a] PAI-1 for PAI-1 antigen assay, COASET[a] PAI for PAI-1 activity assay.

Lipid profiles, including total cholesterol, triglycerides, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol were determined using automate analyzer (Integra 400 plus, Roche Diagnostics GmbH, Mannheim, Germany), which analyzed by the special laboratory at King Chulalongkorn Memorial Hospital.

All data were analyzed using the Statistical Package for the Social Science (SPSS). Differences at significance level of $p<0.05$ were considered to be significant. The distribution of data was test either it was normal distribution or not. Normal distribution used paired t-test for comparing values after exercise with baseline values, unpaired t-test for comparing between control and experimental group. If data are non-normally distributed, nonparametric analysis was used, Wilcoxon Signed-Ranks test for comparing values after exercise with baseline values within group and Mann-Whitney U-test for comparing between control and experimental group.

Results

Thirty six subjects were enrolled in the present study. Only 33 subjects completed the study. Three out of eighteen subjects in the control group had dropped out from the study due to two infection cases and one missing case at the final test. In the experimental group 18 patients enrolled and completed the study. All patients had more than a 6–month history of CAD with either unstable angina or ischemic heart diseases. The baseline demographic data of control and experimental group such as body mass index (BMI), heart rate and VO_{2peak} are shown in Table 1. The average age (SD) of the experimental and control group was 58.0 (7.0), and 58.0 (8.5) years, respectively. There were no significant differences on age, BMI, heart rate, and VO_{2peak} when compared between two groups.

Table 1. Demographic data of control and experimental group

Parameter	Control (n=15)X (SD)	Experiment (n=18)X (SD)
Age (yr)	58.0 (7.0)	58.0 (8.5)
BMI (kg/m^2)	27.2 (3.2)	25.1 (3.2)
Heart rate (beat/min)	73.5 (13.5)	73.6 (13.4)
VO_{2peak} (mL/kg/min)	22.1 (7.6)	19.9 (6.8)

Effect of cardiac rehabilitation program on VO_{2peak}

The effect of the cardiac rehabilitation program on VO_{2peak} (Table 2) was determined at pre-training and post-training in all subjects. The result showed the significant improvement of VO_{2peak} from 19.9 (6.8) to 23.4 (7.6) ml/kg/min in the experimental group ($p<0.05$) and significant decrease from 22.1 (7.6) to 19.2 (6.7) ml/kg/min in the control group ($p<0.05$).

In the experimental group, the average attention rate was 90%, raging from 80% to 100% of training program. After the cardiac rehabilitation program the authors found a significant lower resting heart rate and higher VO_{2peak} when compared to the baseline.

Effects of cardiac rehabilitation program on lipid profile

Comparison of serum lipid profile (total cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol) between the control group and experiment group showed no significant difference before training but after training in both groups. However, triglyceride levels in experimental group were decreased from 135.3(67.9) mg/dl in pre-training to 108.1(39.9) mg/dl in post-training with the significant difference at $p<0.05$ as shown in Table 3.

Table 2. Physical characteristics of subjects before and after 8 weeks of cardiac rehabilitation program

Parameter	Control mean (SD)		Experiment mean (SD)	
	Pre-training	Post-training	Pre-training	Post-training
Heart rate (beat/min)	73 (13.5)	69 (10.7)	73 (13.4)	68(13.0)
BMI (kg/m^2)	27.2 (3.2)	27.3 (3.5)	25.1 (3.2)	24.9(3.2)*
VO_{2peak} (mL/kg/min)	22.1 (7.6)	19.2 (6.7)*	19.9 (6.8)	23.4(7.6)*

* Significant difference within group ($p<0.05$)

Table 3. Lipid profile parameter before and after 8 weeks training at the cardiac rehabilitation program. Data were expressed as mean (SD)

Parameter	Control mean (SD)		Experimental mean (SD)	
	Pre-training	Post-training	Pre-training	Post-training
Cholesterol	181.0 (33.1)	173.7 (29.1)	167.3 (35.8)	164.2 (35.8)
TG	130.3 (73.7)	111.7 (55.4)	135.3 (67.9)	108.1 (39.9)*
HDL-C	48.9 (9.7)	48.2 (10.4)	48.4 (12.1)	50.2 (12.0)
LDL-C	106.6 (26.9)	114.9 (24.8)	98.4 (30.4)	99.5 (28.7)

* Post-training triglyceride was significantly decreased from pre-training at the level $p<0.05$

Table 4. Fibrinolysis parameters before and after 8 weeks training at the cardiac rehabilitation program

Parameter	Control mean (SD)		Experiment mean (SD)	
	Pre-training	Post-training	Pre-training	Post-training
t-PA antigen (ng/mL)	8.2 (4.3)	7.6 (3.1)	7.4 (3.9)	7.5 (2.9)
t-PA activity (IU/mL)	2.1 (1.7)	1.9 (0.9)	2.2 (0.5)	2.3 (0.8)
PAI-1 antigen (ng/mL)	51.4 (14.7)	51.7 (20.8)	51.2 (19.1)	51.5 (16.1)
PAI-1 activity (AU/mL)	17.1 (7.6)	17.7 (11.4)	17.9 (10.8)	16.3 (3.7)

Effects of cardiac rehabilitation program on fibrinolytic parameter

No significant differences in t-PA levels (both antigen and activity), and PAI-1 levels (both antigen and activity) were observed in experimental and control groups after the exercise training for 8 weeks as compared to the baseline as shown in Table 4.

However, significant improvement of fibrinolysis, via decrease of PAI-1 activity level and increase of t-PA activity and t-PA antigen in experimental group were observed when compared between pre-acute sub-maximum exercise ($65\%VO_{2peak}$) and post-acute sub-maximum exercise ($65\%VO_{2peak}$) on the last day of 8 week training of the cardiac rehabilitation program as show in Table 5.

Table 5. Fibrinolysis parameters compared between pre acute and post-acute submaximum exercise ($65\%VO_{2peak}$) on the last day of 8 week training of the cardiac rehabilitation program in experimental group

Parameter	Pre-training mean (SD)	Post-training mean (SD)
t-PA antigen (ng/mL)	7.5 (2.9)	9.2 (2.7)*
t-PA activity (IU/mL)	2.3 (0.8)	2.7 (0.5)
PAI-1 antigen (ng/mL)	51.5 (16.1)	45.7 (16.1)*
PAI-1 activity (AU/mL)	16.3 (3.7)	14.8 (6.3)*

* Significant difference at the level $p< 0.05$

Discussion

Cardiac rehabilitation program is an essential component of the long-term comprehensive management strategy for CAD patients. It reduced the risk factor of disease, improved quality of life and reduced the incident of recurrent disease.

The present study demonstrates the influence of exercise in the rehabilitation program on fibrinolysis in CAD patients. The effect of exercise at light-moderate intensity for 8 weeks on fibrinolytic system was determined by plasma t-PA activity, t-PA antigen, PAI-1 activity, and PAI-1 antigen in CAD patients who have more than 6 months of unstable angina or ischemic heart disease history. They underwent the cardiac rehabilitation program for 8 weeks, 4 days per week, 30 minutes per day, 10 minutes warming up and 10 minutes cooling down before and after exercise respectively. During exercise session heart rate and blood pressure were monitored. After eight weeks of training, the physical fitness was improved in terms of $VO_{2\,peak}$, decreased resting heart rate, and decreased serum triglyceride.

Increased $VO_{2\,peak}$ in the experimental group and decreased in the control group were observed when compared before and after 8 weeks. The data suggested the exercise effects on enhancement of functional capacity of cardiovascular system in CAD patients. This result was consistent with the previous reports by others. Savage et al [14] found 21.2% improvement of $VO_{2\,peak}$ in CAD patients after 4 months of cardiac rehabilitation program. Milani and Lavie [15] also showed an increase in $VO_{2\,peak}$ by 12% after three months of cardiac rehabilitation program.

Level of serum triglyceride in the experimental group was decreased by 20.11% ($p<0.02$) after 8 weeks of training without the changes in dosage of lipid lowering drugs during participation in the program. The present study showed earlier improvement of serum triglyceride from participating in the cardiac rehabilitation program when compared with the study of Paramo et al.[16]. They showed the reduction of serum triglyceride in acute myocardial infarction patients who were enrolled in a 3 months program. The results demonstrated that exercise adherence in CAD patients would help decrease the dosage of lipid lowering drugs. The fibrinolytic parameters including t-PA activity, t-PA antigen, PAI-1 activity, and PAI-1 antigen after eight weeks exercise training at light-moderate exercise intensity were not changed in the CAD patients. Acute changes in fibrinolysis was only observed for a brief period immediately post-exercise [17]. Since the fibrinolysis is part of the hemostasis balance, the reference values in healthy individuals and patients should be reports. However, the authors found a range of variation of these parameters in different studies as follows. Weiss et al [18], showed activation of coagulation and fibrinolysis after cardiac rehabilitation in patients with CAD presented t-PA antigen levels ranged between 5.0 and 22.6 ng/ml and PAI-1 antigen levels ranged between 5.7 and 6.2 ng/ml.

Paramo et al [16], studied the influence of cardiac rehabilitation program in acute myocardial infarction reported the t-PA antigen level ranged between 8.6 and 9.1 ng/ml, PAI-1 activity level ranged between 13.1 and 19.6 AU/ml and PAI-1 antigen level ranged between 36.9 and 43.1 ng/ml.

A similar variation was also seen in the acute effect of exercise on fibrinolytic parameters in other groups as follows.

Womack et al [19], demonstrated fibrinolytic response to acute exercise in patients with peripheral arterial disease as t-PA activity increased by 180% (0.5 $\pm$ 0.16 IU/ml at baseline to 1.4 $\pm$ 1.2 IU/ml at immediately post exercise) and remained significantly elevated 30 min (0.9 $\pm$ 0.4 IU/ml) and 60 min (0.9 $\pm$ 0.3 IU/ml) after exercise. There was a trend for decrease in PAI-1 antigen after exercise (33.4 $\pm$ 33.3 ng/ml at baseline to 26.8 $\pm$ 26.2 ng/ml after exercise). Plasma PAI-1 activity decreased by 43% (2.0.6 $\pm$ 5.5 AU/ml baseline to 11.8 $\pm$ 6.2 AU/ml after exercise), and remained decreased by 36% (13.1 $\pm$ 2.2 AU/ml) 30 min. after exercise and 49% (10.6 $\pm$ 5.2 AU/ml) 60 min. after exercise.

Lin et al.[20], reported activation and disturbance of blood hemostasis following strenuous physical exercise in healthy men. The results showed that t-PA activity level exhibited a significant increase in response to exercise (ranged between 0.71 and 7.24 IU/ml). Comparable changes in t-PA antigen were also observed (ranged between 7.45 and 70.09 ng/ml). The values of t-PA activity and antigen had returned to pre-exercise levels 2 hours after exercise and remained at baseline value over the following 24 hours. A significant decrease in PAI-1 activity was observed immediately after exercise in all subjects (ranged between 4.11 and 19.64 AU/ml).

In conclusion, the present study demonstrated the activation of fibrinolytic system by acute exercise. The cardiac rehabilitation training augmented the physical fitness and decreased serum triglyceride levels. The variation of training program such as intensity, duration, frequency, and studied population were the factors related to the fibrinolysis level.

The baseline data of each parameter in fibrinolysis system should be normalized to be the reference data. There were many more variations in several studies as mentioned above.

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ผลของกิจกรรมการฟื้นฟูหัวใจต่อระบบการแข็งตัวของเลือดในผู้ป่วยโรคหลอดเลือดหัวใจ

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จุดมุ่งหมายของการศึกษา เพื่อดูอิทธิพลของการออกกำลังกายในโปรแกรมฟื้นฟูสมรรถภาพหัวใจต่อการละลายลิ่มเลือด ในผู้ป่วยโรคหลอดเลือดหัวใจ โปรแกรมการฟื้นฟูสมรรถภาพ หัวใจมีความสำคัญต่อการเพิ่มคุณภาพชีวิต และลดอุบัติการณ์ของการเป็นโรคซ้ำ โปรแกรมนี้ใช้การออกกำลังกาย 8 สัปดาห์, 4 วันต่อสัปดาห์, 30 นาทีต่อวัน ที่ความหนักในระดับเบาถึงปานกลาง ผู้ป่วยโรคหลอดเลือดหัวใจจำนวน 33 คน ที่เข้าร่วมโครงการศึกษานี้ เป็นผู้ป่วยโรคหลอดเลือดหัวใจ ที่รับการรักษาที่ โรงพยาบาลธรรมศาสตร์ เฉลิมพระเกียรติ และโรงพยาบาลจุฬาลงกรณ์ ซึ่งมีอายุอยู่ระหว่าง 40 ปี ถึง 70 ปี โดยสุ่มแยกเป็น 2 กลุ่ม คือ กลุ่ม ควบคุม และกลุ่มทดลอง ผลการทดลองแสดงให้เห็นว่า ไม่มีความแตกต่างกันอย่างมีนัยสำคัญของระดับ ทิชชู พลาสมิโนเจน แอกติวิเตอร์ (ทั้งแอนติเจน และ แอกติวิตี) พลาสมิโนเจน แอกติวิเตอร์ อินฮิบิเตอร์ วัน (ทั้งแอนติเจน และ แอกติวิตี) เมื่อเปรียบเทียบก่อนและหลังการฝึกการออกกำลังกาย 8 สัปดาห์ อย่างไรก็ตาม ภายหลังเสร็จสิ้นการฝึกที่ 8 สัปดาห์ พบการเปลี่ยนแปลงที่ดีขึ้น ของปัจจัยการละลายลิ่มเลือด โดยมีการลดลง ของระดับพลาสมิโนเจน แอกติวิเตอร์ อินฮิบิเตอร์ วัน จาก 16.3 (3.7) เป็น 14.6 (6.3) อาร์บิทารี ยูนิต ต่อมิลลิลิตร (ที่ระดับนัยสำคัญ เท่ากับ 0.024) และมีการเพิ่มขึ้นของทิชชู พลาสมิโนเจน แอกติวิเตอร์ แอกติวิตี จาก 2.3(0.8) เป็น 2.7(0.5) อินเตอร์เนชั่นแนล ยูนิต ต่อมิลลิลิตร และมีการเพิ่มขึ้นของทิชชู พลาสมิโนเจน แอกติวิเตอร์ แอนติเจน จาก 7.5(2.9) เป็น 9.2(2.7) นาโนกรัม ต่อมิลลิลิตร (ที่ระดับนัยสำคัญ เท่ากับ 0.01) ในกลุ่มทดลอง เมื่อเปรียบเทียบก่อนและหลังออกกำลังกาย ที่ระดับความหนัก 65 เปอร์เซ็นต์ของการใช้ออกซิเจนสูงสุด พบว่ามีการเปลี่ยนแปลงในทางที่ดีขึ้นของ ความสามารถสูงสุดของการใช้ออกซิเจน อัตราการเต้นของหัวใจขณะพัก และระดับไตรกลีเซอร์ไรด์ในเลือดอย่างมีนัยสำคัญทางสถิติหลังฝึก 8 สัปดาห์ การศึกษาครั้งนี้แสดงให้เห็นว่า ผู้ป่วยโรคหลอดเลือดหัวใจที่เข้าร่วม โปรแกรมออกกำลังกายฟื้นฟูสภาพหัวใจ ระดับความหนักเบาจนถึงปานกลาง มีการเปลี่ยนแปลงในทางที่ดีขึ้นของสมรรถภาพทางกาย และสุขภาพร่างกาย ถึงแม้ว่าไม่มีการเปลี่ยนแปลงที่มากพอจนมีผลอย่างมีนัยสำคัญทางสถิติของปัจจัยการละลายของลิ่มเลือดจากการฝึก 8 สัปดาห์ ผู้ป่วยโรคหลอดเลือด หัวใจควรได้รับการแนะนำให้เข้าร่วมในโปรแกรมออกกำลังกายฟื้นฟูสภาพหัวใจนี้ ซึ่งจะไม่ได้รับอันตรายจากการ เปลี่ยนแปลงของ การทำงานของการละลายลิ่มเลือด แต่การออกกำลังกายยังทำให้ผู้ป่วยมีสุขภาพดีขึ้น