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The Effects of Exercise Training on Resting Prostacyclin and Thromboxane A_2 in Older Adults

Richard D. Kauffman, Gary S. Sforzo, Blaise Frost, and Mikel K. Todd

Ten adult volunteers participated in 16 weeks of cardiovascular exercise training (EG) to determine the effects of training on resting prostacyclin (PGI_2) and thromboxane A_2 (TXA_2). Six volunteers of similar age served as sedentary controls (CG). Blood was collected in tubes after training and eicosanoids were measured by standard ^{125}I RIA methods. Over the 16 weeks of the study, PGI_2 decreased 48% for EG and 33% for CG. There were no between-group differences for PGI_2 values. No significant within-group changes in TXA_2 were found, whereas between-group pretraining TXA_2 values were significantly different. A time main effect for PGI_2 may indicate a seasonal shift in this eicosanoid; however, the additional 15% decrease in PGI_2 for EG may be due to a training-induced reduction in PGI_2 substrate and/or endothelial sensitivity to agonists. The lack of within-group changes in TXA_2 may be due to a combination of high platelet turnover and a training stimulus inadequate to alter platelet function.

Key Words: exercise training, prostacyclin, thromboxane A_2

Prostacyclin (PGI_2) and thromboxane A_2 (TXA_2) are two circulating eicosanoids that influence platelet function. PGI_2 is produced by the vascular endothelium and inhibits platelet activation, whereas TXA_2 is produced by the platelet membrane and stimulates platelet aggregation. Due to their opposing roles in maintaining a hemostatic balance, the ratio between these two eicosanoids may be an indicator of a predisposition to platelet aggregation (Giani, Masi, & Galli, 1985; Moncada, 1988) and related clinical manifestations such as atherogenesis and ischemia (Colman, 1982; Jorgensen & Dyerberg, 1980; Mehta, Mehta, & Horalek, 1983).

Atherosclerosis and ischemic events are more prevalent in older populations, which has prompted researchers to evaluate the effects of advancing age on PGI_2, TXA_2 and PGI_2/TXA_2 ratios. There is some evidence to suggest that PGI_2 concentrations decrease with age (Kent, Kitchell, Shand, & Whorton, 1981), while TXA_2 production either increases (Reilly & Fitzgerald, 1986) or remains unchanged (Vericel et al., 1988).

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Further evidence suggests that acute exercise alters PGI_2/TXA_2 ratios (Carter, Ready, Singroy, Duta, & Gerrard, 1989; Taniguchi, Furui, Yamauchi, & Sotobata, 1984). Both PGI_2 and TXA_2 have been shown to increase during and following acute exercise (Laustiola, Seppala, Nikkari, & Vapaatalo, 1984; Mehta et al., 1983). Other studies have shown significantly greater post exercise TXA_2, whereas PGI_2 concentrations were unchanged (Chen, Jen, & Chang, 1992; Todd, Goldfarb, & Boyer, 1992). The combined effects of age and exercise may further predispose one to cardiovascular complications by altering the eicosanoid balance (Todd, Goldfarb, Kauffman, & Burleson, 1994).

Exercise training may induce physiological mechanisms to increase PGI_2/TXA_2 ratios and reduce the risks of cardiovascular complications. Researchers found more favorable PGI_2/TXA_2 ratios in exercise-trained rats when compared to sedentary controls (Chen, Jen, & Chang, 1993; Merola, Gillispie, Karpen, Panganamala, & Davis, 1984). Another group of researchers (Rauramaa et al., 1984) reported increased PGI_2/TXA_2 ratios in healthy middle-aged men following training. The scant research involving exercise training and eicosanoids suggests a protective mechanism against cardiovascular disease; however, it is unclear if older adults are likely to benefit from the training adaptations. Thus, the purpose of this investigation was to determine the effects of 16 weeks of exercise training on the stable metabolite concentrations of PGI_2 and TXA_2 and on PGI_2/TXA_2 ratios in older adults.

Methods

SUBJECTS

Seven female and 3 male volunteers (68.4 ± 1.3 years old) participated in the exercise training group (EG), while 2 female and 4 male volunteers (64.3 ± 2.3 years old) participated in a sedentary control group (CG). The EGsubjects were recruited from a larger exercise training study conducted in Ithaca, New York, whereas the CG subjects were recruited and tested at West Chester University in Pennsylvania. Unfortunately, the maximal exercise testing protocols used with the EG were unavailable for use with the CG subjects. This resulted in the adoption of different procedures for determining VO_2max in the experimental and control groups. Regardless of group assignment, each subject provided medical and exercise histories prior to participation. Subjects were all nonsmokers and had no known history of atherosclerotic or metabolic diseases. Subjects did not take any medications known to influence eicosanoid synthesis (e.g., nonsteroidal anti-inflammatory agents). Prior to testing, subjects provided informed consent in a manner approved by internal review boards of West Chester University and Ithaca College.

EXERCISE TESTING AND TRAINING

Each EG subject participated in two maximal exercise tests conducted prior to and following 16 weeks of aerobic exercise training. Maximal oxygen consumption (VO_2max) was measured with a treadmill test modified from the branching protocol recommended by the American College of Sports Medicine (1991). During the first 8 weeks of training, EG subjects exercised for 20 min at a heart rate corresponding

to 50% VO_2max. Each EG subject's VO_2 was reassessed with submaximal testing substituted following the first 8 weeks of training. Submaximal tests were stopped when the subjects reached 85% of their previously determined maximum heart rate. Subsequent training intensities were adjusted accordingly. During the next 4 weeks, EG subjects exercised for 30 min at a heart rate corresponding to 65% VO_2max. During the final 4 weeks of the training program, they exercised for 45 min at a heart rate corresponding to 75% VO_2max. Subjects from the EG participated in three exercise sessions a week during training. After 5 to 10 min of light warm-up exercises, exercise sessions involved a circuit of treadmill, cycle, rowing, and upper body ergometry, with lower body exercise always occupying at least 75% of exercise time.

The CG subjects participated in no habitual physical activity within several months prior to and during the study. These subjects met the researchers for testing on four separate occasions. Each subject participated in two modified Astrand–Ryhming submaximal exercise tests (Siconolfi, Cullinane, Carleton, & Thompson, 1982) within 2 weeks prior to the 16-week period and two identical tests within 2 weeks following the 16-week period. Exercise testing, heart rates, and blood pressures for CG were done in duplicate to help ensure the reliability of this mode of testing. Testing of CG was always conducted at the Human Performance Laboratory between 7 and 11 a.m.

The submaximal protocols utilized to estimate VO_2max in the control subjects lack the precision associated with the direct assessment of VO_2max used with the training group. Accordingly, caution is warranted when comparing VO_2max values across the two groups. Despite these limitations, we believe that the advantage of including a sedentary control group in our design outweighs the disadvantages associated with the different testing protocols.

BLOOD SAMPLING

Blood samples were drawn during the week prior to and during the week following participation in the training program. Samples were drawn at the same hour of the day before and after the 16-week period for each subject. Subjects abstained from food and caffeine intake for at least 6 hr prior to sampling. Samples were drawn following 15 min of supine rest. During sample collection, 30 ml of whole blood was drawn into three separate 10-ml Vacutainer tubes.

Blood drawn into the first Vacutainer tube was not used for eicosanoid analysis. Samples used for eicosanoid determination were collected with 10 µl of a 15% ethylenediaminetetraacetic acid (EDTA) solution and 10 µl of a 0.4% acetylsalicylic acid solution. Approximately 2 ml of whole blood was used for determination of hematocrit and hemoglobin. The remaining blood from the tubes containing anticoagulants was centrifuged immediately at 2,500–3,000 rpm for 10 min. The plasma supernatants were removed from these tubes and frozen at –30 °C until assayed.

ANALYSIS OF BLOOD

All pre- and posttraining period eicosanoids for both groups were extracted from plasma and subsequently analyzed in the same assay. The researchers were made

unaware of group assignment throughout all plasma extractions and analyses. Amprep ^2C 100 mg Microcolumns (Amersham Life Sciences, Inc.) were used for 6-keto-$PGF_{1\alpha}$ extraction. Plasma was thawed and acidified to pH 3.5 with citric acid. The microcolumns were conditioned with 2 ml of methanol followed by 2 ml of doubly distilled water at a flow rate of 5 ml/min with the use of an automated syringe pump. Plasma samples were applied to the columns at a flow rate of 3 ml/min. The columns were subsequently washed with 5 ml of water, followed by 5 ml of 10% ethanol, followed by 5 ml of hexane at a flow rate of 3 ml/min. The final fraction containing 6-keto-$PGF_{1\alpha}$ was eluted with 5 ml of methyl formate at a flow rate of 3 ml/min. The final elutions were collected in siliconized glass tubes and dried under vacuum.

An organic extraction (Greaves & Preston, 1982) was performed for TXB_2. Plasma samples were acidified to pH 3.0 with citric acid and subsequently extracted twice with six volumes of cyclohexane:ethyl acetate (1:1, v/v). The organic layers were pooled and dried under vacuum. Following the initial extractions, plasma concentrations of 6-keto-$PGF_{1\alpha}$ and TXB_2 were determined by specific ^{125}I radioimmunoassay. Eicosanoid assays were conducted according to the procedures outlined by PerSeptive Diagnostics, Inc. The 6-keto-$PGF_{1\alpha}$ and TXB_2 concentrations were adjusted for plasma volume changes (Dill & Costill, 1974) that occurred between pre- and posttraining program sampling.

STATISTICAL ANALYSES

Means ± standard errors for subjects' exercise and resting characteristics, 6-keto-$PGF_{1\alpha}$ concentrations (pg/ml), TXB_2 concentrations (pg/ml), and the 6-keto-$PGF_{1\alpha}$/TXB_2 ratios are reported. A repeated-measures analysis of variance (ANOVA) was employed to analyze within- and between-group data. A Neuman Keul's post hoc technique was subsequently employed to elucidate differences between pairs of data. Analysis of covariance (ANCOVA) was performed to determine if there were any between-group differences in eicosanoid concentrations and ratios following the training period that were independent of pretreatment between-group differences. Statistical significance and the associated alpha level are indicated where applicable.

Results

The VO_2max for EG increased 13%, from 22.62 ± 1.89 ml/kg/min pretraining to 25.98 ± 2.11 ml/kg/min ($p < .05$) posttraining (Table 1). Correspondingly, hemoglobin counts for EG increased significantly from 13.41 ± 0.35 pretraining to 14.49 ± 0.23 ($p < .05$) posttraining. Estimated VO_2max for CG did not change significantly, from 19.96 ± 3.93 ml/kg/min pretraining to 20.30 ± 3.09 ml/kg/min posttraining. The VO_2max estimates for CG from each of the two submaximal exercise tests performed prior to the 16-week period were highly correlated ($r = .98$; $p < .05$), as were estimates from the two exercise tests performed following the 16-week period ($r = .98$; $p < .05$). Hemoglobin counts for CG were not significantly altered, from 13.79 ± 0.99 pretraining to 14.45 ± 0.36 posttraining. Prior to the study period, the highest workloads and highest heart rates reached by CG during one of the submaximal exercise tests were 475.00 ± 60.22 kpm/min and 121.67 ± 4.51

bpm, respectively. Similarly, the corresponding exercise characteristics for CG following the study period were 450.00 ± 38.74 kpm/min and 118.50 ± 3.52 bpm, respectively. There were no significant between-group or within-group differences in weight, resting heart rates, and resting systolic and diastolic blood pressures.

Resting 6-keto-$PGF_{1\alpha}$ for EG decreased from 736.1 ± 72.3 pg/ml prior to training to 370.5 ± 44.2 pg/ml ($p < .05$) following training (Figure 1). For CG, resting 6-keto-$PGF_{1\alpha}$ decreased from 600.0 ± 66.1 pg/ml prior to the 16-week period to 405.0 ± 88.4 pg/ml ($p < .05$) following this period. Concentrations of 6-keto-$PGF_{1\alpha}$ for CG decreased 33% ($p < .05$) following the training period, whereas 6-keto-$PGF_{1\alpha}$ for EG decreased 48% ($p < .05$), or 15% more than CG from pre- to posttraining. No significant differences in 6-keto-$PGF_{1\alpha}$ concentrations between EG and CG were found either before or after the training period.

Prior to the training period, TXB_2 concentrations for EG and CG were 319.7 ± 42.6 pg/ml and 160.7 ± 10.6 pg/ml, respectively ($p < .05$). Following the training period, EG and CG had resting TXB_2 values of 295.9 ± 40.5 pg/ml and 146.7 ± 28.1 pg/ml, respectively. The pretraining TXB_2 was 50% higher for EG than for CG ($p < .05$); similarly, posttraining TXB_2 was 44% higher for EG than for CG. An ANCOVA in which pretraining TXB_2 was used as a covariate revealed significant between-group posttraining differences. The adjusted means for TXB_2 were 268 ± 31 pg/ml for EG and 191 ± 22 pg/ml for CG ($p < .05$). When compared to pretraining concentrations, within-group posttraining TXB_2 for EG and CG decreased 7% and 9%, respectively. These values were not significantly different.

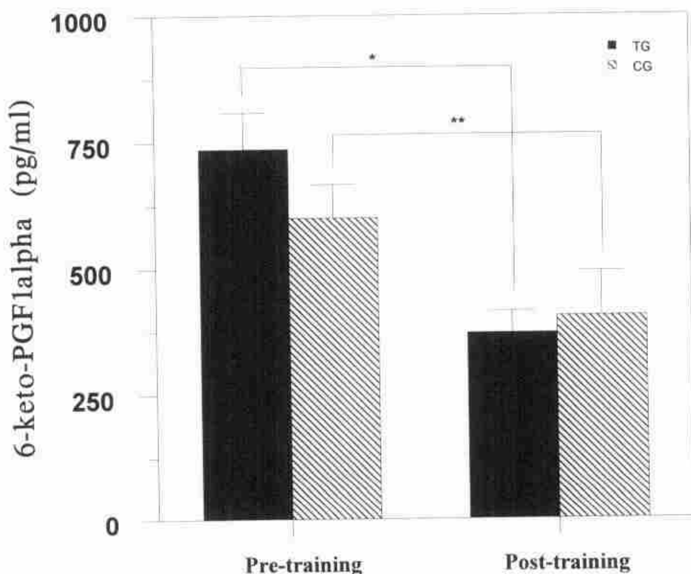


Figure 1. Pre- and posttraining 6-keto-$PGF_{1\alpha}$.

Table 1 Resting and Exercise (VO_2max Only) Characteristics for EG and CG Pre- and Posttraining Period

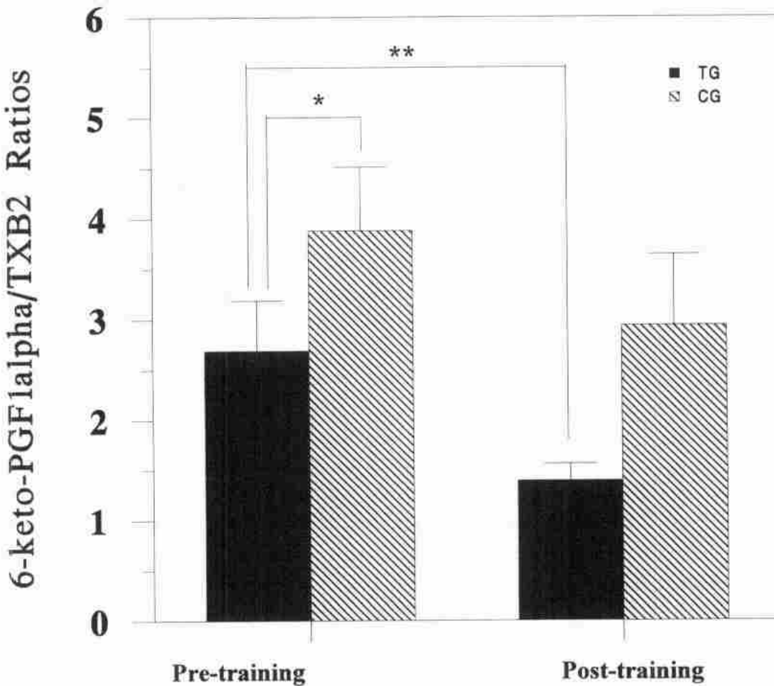
Subject	Age	Weight (kg)		VO_2 (ml/kg/min)		HR (bpm)		SBP (mmHg)		DBP (mmHg)	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
E1	68	74.5	73.2	21.10	25.84	75	68	126	148	74	98
E2	71	75.9	75.5	15.50	18.45	55	58	144	130	80	80
E3	60	80.0	80.5	19.40	24.23	76	71	126	130	68	80
E4	69	75.0	75.5	19.96	20.61	86	89	142	136	88	82
E5	68	65.9	66.8	25.10	28.66	64	67	134	120	68	74
E6	71	71.8	70.9	21.30	21.29	80	70	110	112	80	66
E7	75	81.4	81.4	28.60	29.82	90	78	132	142	74	78
E8	68	88.2	88.6	33.90	38.97	61	60	116	128	78	76
E9	64	75.5	75.5	—	25.98	80	78	152	166	84	84
E10	70	82.7	83.2	18.70	—	75	79	138	130	76	84
Mean	68.4	77.1	77.1	22.62	25.98*	74.2	71.8	132.0	134.2	77.0	80.2
SE	1.3	2.0	2.0	1.89	2.05	3.5	3.0	4.1	4.8	2.0	2.6
C1	58	65.0	65.0	20.15	21.85	68	66	116	118	70	76
C2	59	83.6	76.4	12.86	15.51	84	80	138	134	98	84
C3	72	76.4	76.4	22.45	20.94	63	64	122	124	88	78
C4	68	85.9	84.5	24.33	24.79	51	64	128	128	72	78
C5	62	93.2	94.1	19.10	19.34	72	81	136	136	84	84
C6	67	89.1	89.1	20.88	19.36	60	64	128	124	80	78
Mean	64.3	82.2	80.9	19.96	20.30	66.3	69.8	128.0	127.3	82.0	79.7
SE	2.3	4.1	4.3	1.61	1.26	4.6	3.4	3.4	2.8	4.3	1.4

*Statistically significant from pretraining period value; $p < .05$.

The 6-keto-$PGF_{1\alpha}$/TXB_2 ratios for each subject were calculated from their measured concentrations and are reported as group mean ratios (Figure 2). Pretraining period ratios for EG and CG were 2.69 ± 0.50 and 3.88 ± 0.63 ($p < .05$), respectively. The EG pretraining ratio was 31% lower ($p < .05$) than the CG pretraining ratio. Posttraining ratios for EG and CG were 1.39 ± 0.16 and 2.94 ± 0.70, respectively. The EG posttraining ratio was 53% lower ($p < .05$) than the CG posttraining ratio. When the pretraining ratios were used as covariates, between-group differences in posttraining ratios were not significantly different. The posttraining ratio for EG subjects was 48% lower ($p < .05$) than their pretraining ratio. The posttraining ratio for CG subjects, although 24% lower than their pretraining ratio, was not significantly different.

Discussion

The VO_2max and hemoglobin counts for EG increased significantly following the training period, suggesting that aerobic adaptations to training occurred. No



* **ANOVA (p < 0.05)

Figure 2. Pre- and posttraining 6-keto-$PGF_{1\alpha}$/TXB_2 ratios.

changes in estimated VO_2max for CG were found with respect to the 16-week period during which they remained sedentary. Additionally, there were no changes in resting heart rates, blood pressures, and highest workloads and heart rates achieved by CG during the two submaximal exercise tests, suggesting that the 16-week period did not alter the control subjects' fitness levels.

The significant decline in the 6-keto-$PGF_{1\alpha}$ concentrations for EG may be partly attributable to the exercise training regime. The EG eicosanoid ratios decreased significantly after exercise training, whereas the CG ratios did not. Clearly, the decline in the eicosanoid ratios following exercise training was primarily due to a reduction in 6-keto-$PGF_{1\alpha}$. In order to more thoroughly compare the data in this study with those reported by other researchers, the individual constituents, 6-keto-$PGF_{1\alpha}$ and TXB_2, will be discussed separately.

Merola et al. (1984) found no significant differences in 6-keto-$PGF_{1\alpha}$ produced in aortas of exercise-conditioned rats when compared to sedentary controls of unspecified ages. However, the coronary vascular compartments of the trained rats had a greater sensitivity to exogenous PGI_2 doses than those of the sedentary controls, suggesting that coronary artery sensitivity may be the result of PGI_2 receptor up-regulation or an enhanced PGI_2/receptor interaction. With respect to the current study, it may follow that endothelial cells will adapt to a greater sensitivity of the vessels by producing less PGI_2.

In contrast, Rauramaa et al. (1984) found significantly greater 6-keto-$PGF_{1\alpha}$ in healthy men, 32 to 44 years old, who walked and jogged at a low to moderate intensity for 8 weeks. These authors attributed the increase in 6-keto-$PGF_{1\alpha}$ to a concomitant increase in HDL. Serum lipoproteins were not measured in the present study. One major difference in this study and the one conducted by Rauramaa et al. (1984) was the ages of the subjects. Such differences may help explain the different findings in the studies.

Additionally, Chen et al. (1993) found significantly greater resting concentrations of 6-keto-$PGF_{1\alpha}$ produced by thoracic aortas of trained rats when compared to sedentary controls. Several factors may account for the discrepancy between the present study and the one conducted by Chen et al. (1993). For example, Chen et al. (1993) used relatively young laboratory animals and a more vigorous training regime. One must recognize that PGI_2 production in young rats and older humans may vary considerably. The vascular compartments in older humans are subject to endothelial damage (i.e., fatty streaks and plaque) associated with subclinical manifestations of cardiovascular disease (Ross, 1986). Furthermore, Chen et al. (1993) measured 6-keto-$PGF_{1\alpha}$ synthesized by aortic tissue, whereas in the present study, venous 6-keto-$PGF_{1\alpha}$ concentrations are representative of PGI_2 production throughout the vascular system.

No significant alterations were found for TXB_2 within either group respective of the 16-week period. Between-group TXB_2 was significantly different before and after the training period in both groups, with EG having the higher concentrations. Because subjects were not randomly selected and assigned, there is an increased likelihood that initial differences are attributable to group variations not controlled by randomization. However, there is no evidence to support the effects of geography, sex, or other such variations on eicosanoid concentrations among groups of individuals. Therefore, nonrandom group assigment should be adequate for such a physiological study. The posttraining difference is not likely to be attributable to

training since both groups had a slight, but insignificant, decrease in TXB_2 following the exercise training program.

Merola et al. (1984) and Chen et al. (1992) found significant reductions in TXB_2 in exercise-trained rats when compared to sedentary controls. Additionally, Merola et al. (1984) found that training reduced thrombin-stimulated TXB_2 synthesis in washed platelets from exercise-trained rats. Rauramaa et al. (1984) reported a significant reduction in resting TXB_2 in a group of middle-aged men after 8 weeks of mild-intensity exercise training. Exercise training has also been shown to reduce resting concentrations of plasma ß-thromboglobulin, a marker of platelet activation, and the sensitivity of platelets to agonist-induced aggregation in vitro (Davis, Boyd, McKinney, & Jones, 1990). Platelet counts and platelet activity were not measured in the current study, however. Although there was not a significant reduction in TXB_2 in either group in the present study, the concentrations for each group declined slightly.

The reduction in TXB_2 production found with exercise training can be explained in a number of ways. One group of researchers (Ohnishi et al., 1992) suggested that there is a competition between platelets and endothelial cells for the eicosanoid precursor, arachidonic acid. These researchers reported that when TXA_2 (i.e., the metabolic precursor of TXB_2) synthase activity is blocked, 6-keto-$PGF_{1\alpha}$ concentrations increase, thus suggesting that arachidonic acid or cyclic endoperoxides from platelets are shunted toward the endothelial cells and acted on by PGI_2 synthase. These researchers further suggested that as the sensitivity of TXA_2 agonist receptors diminishes with exercise, the production of TXA_2 also decreases, leaving a greater arachidonic acid pool for PGI_2 production.

Murray and Fitzgerald (1989) studied the molecular events involved in TXA_2 receptor desensitization to repeated stimulation and the subsequent down-regulation of TXA_2 receptors. Their results indicate that desensitization of the platelet TXA_2 receptor is initially mediated by an uncoupling of the TXA_2 receptor and its second messenger system. With repeated exposure to the agonist, which would occur throughout an exercise training period, there is ostensibly greater platelet TXA_2 receptor down-regulation. These data suggest a possible mechanism for a decrease in TXB_2 metabolite following repeated bouts of exercise.

To better understand how PGI_2 and TXA_2 adapt to exercise training, one may consider how these eicosanoids are effected by a single bout of exercise. Numerous researchers have found that acute exercise stimulates PGI_2 and TXA_2 production (Laustiola et al., 1984; Onishi et al., 1992; Todd et al., 1992). Furthermore, several agonists of PGI_2 and TXA_2 are known to increase during acute exercise, including catecholamines, adenine nucleotides, adenosine phosphates, serotonin, and thrombin. Taniguchi et al. (1984) and Wennmalm (1975) suggested that increased catecholamines during acute exercise may elevate plasma eicosanoids. An increase in adenine nucleotides in blood from working muscles has been proposed as a mechanism for increased PGI_2 synthesis during acute exercise (Wennmalm & Fitzgerald, 1988). In addition, Frangos, Eskin, McIntire, and Ives (1985) reported that flow-induced shear stress augmented 6-keto-$PGF_{1\alpha}$ synthesis in cultured endothelial cells. Thus, increased blood flow that occurs during exercise may further stimulate endothelial formation of PGI_2. Although the effects of exercise on other eicosanoid agonists are still unclear, the repeated stimulation of PGI_2 and TXA_2 synthesis associated with exercise training may lead to down-regulation of

agonist receptors on the endothelial and platelet surfaces as well as uncoupling of second messanger systems. These receptor-mediated events may ultimately result in lower resting eicosanoid concentrations. The results of the present study concur with this explanation. Although a lower PGI_2 may favor platelet activation, especially when PGI_2/TXA_2 ratios decrease, there is evidence that increased fibrinolytic and tissue plasminogen activator activity may counter any increase in platelet activation (Davis et al., 1990; Rankinen, Vaisanen, Penttila, & Rauramaa, 1995).

It may also be important to consider the turnover rate or life span of platelets and endothelial cells when evaluating the effects of exercise training on eicosanoid production. Circulating platelets are relatively short-lived, with a life span of 9 to 12 days, whereas endothelial cells have a much greater life span (Zucker-Franklin, Greaves, Grossi, & Marmont, 1988). One might reason that in light of the short life span of platelets, moderate training 3 days per week as in the present study may be inadequate to stimulate long-term alterations in platelet production of TXA_2. In contrast, endothelial cells would likely survive the duration of a training program similar to the one used in the present study, therefore having an increased exposure to exercise training.

The results of the present study indicate that 6-keto-$PGF_{1\alpha}/TXB_2$ ratios may decrease in older adults as a result of cardiovascular exercise training. This change is attributable primarily to a significant reduction in circulating concentrations of 6-keto-$PGF_{1\alpha}$. Although these data suggest that older adults may be more predisposed to platelet aggregation following exercise training, other data suggest that sensitivity to PGI_2 may be enhanced with training, thus countering the lower endogenous PGI_2 production. Further research concerning exercise training and eicosanoids is necessary for a more complete understanding of the mechanisms involved in excessive platelet aggregation and cardiovascular disease as well as the adaptations to chronic exercise in older adults.

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