Regular Resistance Training Enhances Fibrinolytic Potential but Does Not Affect Coagulation

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ABSTRACT

NAGELKIRK, P. R., K. SOAVE, C. ALTHERR, and A. DEL POZZI. Regular Resistance Training Enhances Fibrinolytic Potential but Does Not Affect Coagulation. *Med. Sci. Sports Exerc.*, Vol. 53, No. 11, pp. 2318–2323, 2021. Elevated coagulation and/or lowered fibrinolytic activity increases the risk of a thrombotic event, which affects more than 2 million people each year. Resistance training (RT) produces various adaptations that are theorized to influence hemostasis, but research in this area is limited. **Purpose:** This study aimed to identify effects of an 8-wk, whole-body RT program on coagulation and fibrinolysis. **Methods:** Sixteen healthy women and men (23 ± 5 yr) completed an RT program three times per week for 8 wk. Exercises included 2–3 sets of 8–12 repetitions performed at approximately 60%–80% of a one repetition maximum. Strength, body composition, and body circumferences were assessed before and after training. Plasma samples were obtained before and after training, and analyzed for active tissue plasminogen activator (tPA activity), total tissue plasminogen activator (tPA antigen), active plasminogen activator inhibitor-1 (PAI-1 activity), total plasminogen activator inhibitor-1 (PAI-1 antigen), fibrinogen, and coagulation factors VII (FVII) and VIII (FVIII). **Results:** Significant increases in lean mass, arm and thigh circumferences, maximal chest press (PRE: 57.8 ± 37.5 kg, POST: 73.3 ± 43.2 kg), and leg press (PRE: 189.5 ± 96.0 kg, POST: 256.7 ± 97.9 kg) were observed ($P < 0.05$ for all). PAI-1 activity (PRE: 20.3 ± 32.5 $IU \cdot mL^{-1}$, POST 9.5 ± 20.9 $IU \cdot mL^{-1}$) and PAI-1 antigen decreased (PRE: 10.2 ± 9.0 $ng \cdot dL^{-1}$, POST: 7.2 ± 5.7 $ng \cdot dL^{-1}$; both, $P < 0.05$). No change in tPA activity or tPA antigen occurred. Fibrinogen, FVII, and FVIII did not change after training. **Conclusions:** Inhibition of fibrinolysis was decreased after training, and coagulation was unaffected. These results suggest that regular RT may beneficially influence the risk of a thrombotic event. More research is warranted to understand the mechanisms through which RT affects hemostasis. **Key Words:** HEMOSTASIS, THROMBOSIS, PLASMINOGEN, STRENGTH TRAINING

Blood clots induce approximately 2.7 million adverse events every year in the United States, including deep venous thromboses, pulmonary emboli, ischemic strokes, and an estimated 80% of all myocardial infarctions. The basal hemostatic state is dictated by the balance between clotting (i.e., coagulation) and fibrinolysis, the ability to dissolve blood clots. Measures of coagulation and fibrinolysis are independently associated with cardiovascular diseases and their associated sequelae and are implicated in numerous other chronic diseases such as cancer, diabetes, and peripheral arterial disease (1).

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Although acute exercise causes transient increases in thrombotic potential (2,3), regular exercise training is believed to lower coagulation activity and enhance fibrinolytic capacity (4). The overwhelming majority of the research in this area focuses on moderate-intensity endurance exercise training and aerobic fitness (5–9). The mechanisms through which exercise training influences hemostasis are not well understood but may include endothelial adaptations that are caused by exercise-induced increases in vascular shear stress, body composition changes, and/or activity of the renin–angiotensin system (RAS) (10,11).

Acute bouts of resistance exercise have also been shown to cause significant changes in hemostatic potential among various populations (12–14), and regular, chronic resistance training is known to induce some of the physiological adaptations that are theorized to mediate hemostatic adaptations to aerobic exercise training. Improving muscular fitness through resistance training has been shown to improve body composition, enhance insulin sensitivity, and lower blood pressure (15). Markers of hemostasis are influenced by body composition (16), and

fibrinolytic potential, in particular, is associated with insulin resistance (17). Moreover, an inverse relationship between diastolic blood pressure and fibrinolytic activity has been reported (18). Thus, it seems that chronic resistance training may induce mechanistic adaptations that would influence hemostatic balance.

However, little is known about the effects of regular resistance training on thrombotic potential. The literature reveals only a few, small studies that are of cross-sectional design. Baynard et al. (19) reported that resistance-trained men exhibited a smaller decrease in plasma plasminogen activator inhibitor-1 (PAI-1), the primary inhibitor of fibrinolysis, after a maximal treadmill exercise test, than did both endurance-trained and untrained men. These findings seem to conflict with observations from another research group, who demonstrated that resistance-trained men and women exhibit enhanced fibrinolytic activity, as well as diminished platelet activation and prolonged activated partial thromboplastin time in response to an acute, exhaustive resistance exercise test compared with untrained individuals (20,21). Longitudinal studies of hemostatic adaptations to resistance training are lacking.

Therefore, the purpose of the present study was to examine coagulation and fibrinolytic potential before and after an 8-wk, whole-body, resistance training regimen. It was hypothesized that fibrinolytic activity would be increased, and coagulation potential would be decreased after completion of the training program.

METHODS

All study procedures were approved by the institutional review board at Ball State University, and each participant provided signed informed consent before enrollment in the study. Various *a priori* sample size analyses were conducted using data from cross-sectional studies and longitudinal investigations of hemostatic adaptations to regular aerobic exercise. It was estimated that 20 subjects would be sufficient to provide adequate power ($1 - \beta = 0.8$, $\alpha = 0.05$) to observe changes in plasma concentrations of both fibrinolytic and coagulation variables (G*Power version 3.0.10). A cohort of 19 healthy participants were enrolled in the study ($n = 12$ women, $n = 7$ men). Three men withdrew from the study for personal reasons, leaving $n = 16$ subjects (age, 23 ± 1 yr; body mass index, 24.9 ± 5.0 $kg \cdot m^{-2}$) in the sample pool. All participants were free from any known metabolic or cardiovascular diseases and were taking no prescription medications, other than oral contraceptives, that would influence the variables under examination. Participants did not participate in regular resistance training for a minimum of 6 months before enrollment and did not have any physical limitations that would affect their ability to progress the weight resistance throughout the 8-wk training intervention.

Experimental design. Resistance training exercise sessions were performed 3 $d \cdot wk^{-1}$ with the goal of completing 24 sessions in 8 wk. Statistical analyses were conducted only with data from individuals who participated in a minimum of 80% of the training sessions. All 16 participants met this standard and were included in final analyses. Data collection occurred at two different time points: baseline measures were collected within 7 d before beginning the exercise program, and posttraining measures were obtained within 7 d after completing the program. To control for diurnal variations, both data collection sessions were completed at the same time of day for each participant. Female participants were tested during the first 5 d of menses, as self-reported, to control for the influence of sex-specific hormones on the variables under examination. Each participant was free from fever and illness for 7 d before data collection, refrained from exercise and the use of alcohol for 24 h before data collection, and avoided caffeine, food, and other drinks (except water) for 12 h. Data collection included the following measures: maximal upper- and lower-body strength, body composition, circumference measurements, and blood samples for hemostatic analyses. Physical activity and energy expenditure were assessed by 7-d activity recall (22). Strength testing was either performed after all other measures were completed, or on a separate day.

Muscular strength assessment. One repetition maximum (1-RM) tests for the chest and leg press exercises were performed according to American College of Sports Medicine guidelines (23). Briefly, after a warm-up and familiarization period, each subject performed a single repetition lift equal to 50%–70% of the subject's predicted maximum capacity. Resistance was progressively increased per repetition until the participant was unable to complete the selected repetition. The final weight lifted successfully was recorded as the absolute 1-RM.

Anthropometric measures. Body composition was assessed by air displacement plethysmography (BODPOD; Cosmed, Concord, CA). Circumference measurements for eight different anatomical landmark sites (abdomen, arm, buttocks/hips, calf, forearm, hips/thigh, midthigh, and waist) were obtained using standard procedures (23) and by the same investigator to ensure reliability.

Blood sampling/processing. Blood samples were obtained from an antecubital vein using venipuncture with minimal stasis after 20 min of supine rest. A 5-mL "discard tube" was first drawn, after which a 10-mL blood sample was collected in tubes containing ~3.2% 0.105 M sodium citrate. Within 15 min of being collected, blood samples were centrifuged at 1500*g* at 4°C for 20 min. Plasma was decanted from the red blood cells and spun again for 5 min at 1500*g* at 4°C to ensure the sample was free of platelets. Platelet-poor plasma samples were distributed into 0.4 mL aliquots and stored at −80°C until further analysis. Enzyme-linked immunosorbency assays were used to quantify plasma concentrations of total tissue plasminogen activator (tPA antigen; AssayPro AssayMax, catalog no. ET2001-1), unbound active tPA (tPA activity; Molecular Innovations, catalog no. HTPAKT), total PAI (PAI-1 antigen; AssayPro AssayMax, catalog no. EP1100-1), and unbound active PAI-1 (PAI-1 activity; Molecular Innovations, catalog no. HPAIKT) according to the manufacturer's instructions. Samples were batched and analyzed on a single plate for each variable. Assays for plasma concentration of fibrinogen, and coagulation factor VII and factor VIII were performed using an automated coagulation analyzer (STart4®;

Diagnostica Stago, Parsippany, NJ) in accordance with the manufacturer's instructions. Intra-assay coefficients of variability were all ≤5%

Resistance exercise training. Study personnel supervised all resistance training sessions. Each training session included eight exercises targeting all major muscle groups (leg press, leg curls, chest press, lateral row, lat pull down, shoulder press, bicep curls, and triceps extensions). Bicep curls were performed as a free weight exercise, whereas all other lifts were performed on stacked-weight machines. The target intensity for all exercises was 8–12 repetitions until volitional fatigue, which corresponds with 60%–80% of 1-RM (23). The first 2 wk of training consisted of two sets of each exercise with a 2-min rest between sets. At the onset of the third week of training, a third set was added to each exercise with the same repetition range (8–12). Weight was progressed by study personnel as needed to maintain the target intensity.

Statistical analysis. All statistical analyses were conducted using IBM SPSS Statistics for Windows version 27.0 (IBM Corp., Armonk, NY). Subject characteristics were depicted using descriptive statistics. The baseline and posttraining values of the following variables were analyzed by paired *t* tests: anthropometric variables (weight, circumferences, relative body fat percentage), daily energy expenditure (in kilocalories per day), plasma concentrations of fibrinolytic variables (tPA activity, tPA antigen, PAI-1 activity, and PAI-1 antigen), markers of coagulation (fibrinogen, factor VII, factor VIII), and muscular strength. Pearson correlation coefficients were used to assess relationships between lean mass, fat mass, and body composition to the change (delta) in concentrations of plasma markers of coagulation and fibrinolysis. Distribution normality of all variables was assessed using a Shapiro–Wilk test. PAI-1, tPA, and factor VIII data were not normally distributed and were thus log transformed before analysis. Statistical significance was set at $\alpha = 0.05$.

RESULTS

Unless otherwise indicated, all results are expressed as means ± SD. On average, subjects completed 23.1 ± 1.7 training sessions over 7.6 ± 0.8 wk. No significant change in average weekly energy expenditure during moderate- (PRE: 4.2 ± 4.6 kcal·kg^{-1}·d^{-1}, POST: 3.0 ± 4.0 kcal·kg^{-1}·d^{-1}), hard- (PRE: 1.9 ± 4.2 kcal·kg^{-1}·d^{-1}, POST: 3.7 ± 7.5 kcal·kg^{-1}·d^{-1}), or very hard-intensity exercise (PRE: 2.8 ± 4.5 kcal·kg^{-1}·d^{-1}, POST: 1.0 ± 2.2 kcal·kg^{-1}·d^{-1}) were observed (all, $P > 0.05$). Time spent resistance training was greater after the training program (PRE: 3.8 ± 10.0 min, POST: 200.0 ± 79.2 min; $P < 0.05$). Maximal chest and leg press strength significantly increased after training ($P < 0.01$), as shown in Table 1.

Body composition measures are presented in Table 1. Significant increases in mass and lean mass were observed after training ($P < 0.05$), without any measurable differences in relative body fat percentage or fat mass ($P > 0.05$). Arm (PRE: 29.9 ± 5.1 cm, POST: 31.0 ± 5.0 cm; $P < 0.01$) and midthigh circumferences (PRE: 50.0 ± 5.4 cm, POST: 51.1 ± 5.8 cm; $P < 0.01$) were significantly larger after training. No significant changes were found for the following circumference measurements: abdomen (PRE: 83.1 ± 15.7 cm, POST: 82.3. ±15.7 cm), buttock (PRE: 101.4 ± 8.9 cm, POST: 101.4 ± 8.5 cm), calf (PRE: 37.3 ± 3.5 cm, POST: 37.0 ± 3.8 cm), forearm (PRE: 27.2 ± 6.7 cm, POST: 26.2 ± 3.1 cm), hip (PRE: 60.4 ± 7.0 cm, POST: 60.5 ± 7.1 cm), and waist (PRE: 78.3 ± 14.5 cm, POST: 78.3 ± 14.9 cm; all, $P > 0.05$).

The training regimen did not influence measurable change in plasma levels of fibrinogen (PRE: 277.0 ± 58.7 mg·dL^{-1}, POST: 307.4 ± 77.2 mg·dL^{-1}; $P > 0.05$). Nor were there any changes in coagulation factor VII (PRE: 122.3% ± 25.7%, POST: 121.5% ± 38.0% of normal) or factor VIII (PRE: 88.6% ± 47.4%, POST: 97.2% ± 58.2% of normal; both, $P > 0.05$). Plasma concentrations of tPA and PAI-1 are shown in Figures 1 and 2, respectively. No changes in plasma concentrations of the fibrinolytic activator tPA antigen or tPA activity were observed ($P > 0.05$). However, the training program induced significant decreases in concentrations of PAI-1 antigen and PAI-1 activity ($P < 0.05$). The change in PAI-1 activity was significantly and inversely related to baseline lean mass and fat mass ($r = -0.871$ and -0.537, respectively; both, $P < 0.05$). The changes in all other fibrinolytic and coagulation variables were not significantly correlated to any measure of body composition or mass.

DISCUSSION

The purpose of the present study was to examine potential changes in markers of hemostasis after 8 wk of resistance exercise training. The principal finding of this study was a significant reduction in both active and total plasma concentration of PAI-1, which is a potent inhibitor of fibrinolytic activation. This observation did not coincide with proportionate changes to plasma levels of tPA, the primary activator of fibrinolysis. Furthermore, coagulation potential was unchanged following the resistance training regimen, contrary to the original hypotheses.

The PAI-1 adaptations reported here are clinically important, as elevated PAI-1 is associated with venous thromboembolism, metabolic syndrome, hypertension, and risk of stroke

TABLE 1. Anthropometric and maximal strength adaptations to training.

	Full Sample ($n = 16$)	Women ($n = 12$)	Men ($n = 4$)
Weight (kg)	72.8 (19.7)–74.0 (20.5)*	66.1 (7.9)–66.7 (7.5)	92.9 (31.4)–96.1 (32.2)
Body fat (%)	28.0 (8.6)–27.2 (8.2)	28.3 (6.2)–27.4 (5.3)	26.9 (15.1)–26.7 (15.3)
Lean mass (kg)	52.2 (10.0)–53.6 (10.4)*	47.2 (5.5)–48.2 (5.6)	64.4 (10.0)–66.8 (9.7)
Fat mass (kg)	21.6 (12.2)–21.3 (12.5)	18.9 (5.7)–18.5 (4.7)	28.5 (22.1)–29.3 (23.1)
Chest press (kg)	57.8 (37.5)–73.3 (43.2)*	44.0 (8.1)–54.6 (9.6)	99.3 (60.9)–129.5 (58.0)
Leg press (kg)	189.5 (95.8–256.7 (97.9)*	158.5 (51.8)–224.9 (56.1)	282.6 (143.6)–351.8 (142.3)

Data are presented as means (SD).
*Significantly change from baseline to posttraining ($P < 0.05$). Note that sex differences were not analyzed statistically and are presented here for descriptive purposes only.

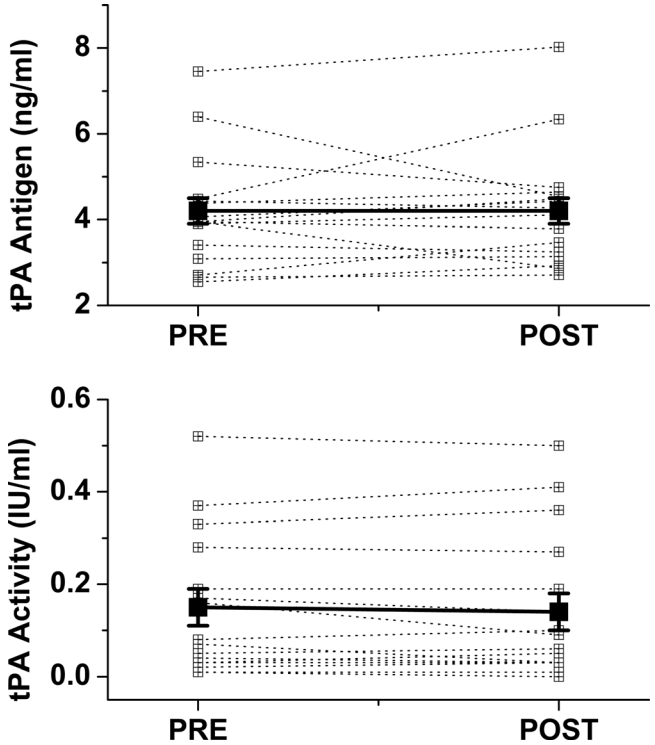

FIGURE 1—Tissue plasminogen activator. Shown are mean ± SE and values from individual participants. PRE, baseline; POST, after 8 wk of resistance training; tPA, tissue plasminogen activator.

and myocardial infarction (18,24–26). Thus, the observed improvement in fibrinolysis may be a mechanism through which resistance training reduces the risk of thrombotic and cardiovascular events. These results affirm cross-sectional reports that resistance-trained individuals have lower PAI-1 concentrations compared with untrained or aerobically trained participants (19,21).

One possible explanation for this observation is the relationship between body composition and fibrinolysis. Adipocytes produce PAI-1, and we observed a statistical relationship between baseline fat mass and the training-induced change in PAI-1 concentration. The influence of body fat on fibrinolytic adaptations to regular exercise training is not entirely clear. Some studies of endurance training that led to reduced body fat also show decreased plasma PAI-1 concentrations (5,6,8). Others report training-induced improvements in fibrinolysis that are statistically independent from body composition changes (27), or, like the present study, changes in PAI-1 without any change in fat mass or relative body fat percentage (28). Fibrinolytic improvements with training might be dependent on abdominal (16) and/or visceral fat deposition (27,29). Additional investigation is needed to elucidate these putative relationships. Lean mass may also contribute to PAI-1 levels. In a small study of the effects of aerobic exercise training on overweight men, Hittel et al. (11) observed a nonsignificant decrease in skeletal muscle PAI-1 gene expression. The increased strength, lean mass, and circumferences of arm and midthigh observed after completion of the training program in the present study likely indicate changes to skeletal muscle mass, which may have modified muscle PAI-1 expression. It should be noted, however, that tPA levels were not affected by the resistance training program in the present study, despite evidence that muscle tPA gene expression is augmented after regular aerobic exercise (11). Furthermore, we did not observe a statistical relationship between the changes in lean mass or fat mass with a change in any of the hemostatic variables under examination. A potential mechanistic relationship between exercise-induced changes to skeletal muscle function, mass, and synthesis of tPA and PAI-1 is purely speculative and bears continued investigation.

A second potential mechanism for the training-induced reduction in PAI-1 relates to the RAS. There is ample evidence that fibrinolytic activity is controlled by the RAS (30). In various *in vivo* and *in vitro* studies, angiotensin II has been shown to stimulate the release of PAI-1 (31,32). Furthermore, pharmacologic inhibition of the RAS leads to reduced concentrations of plasma PAI-1 (33). Resistance training causes hemodynamic adaptations that are theorized to be mediated by the RAS. Animal models suggest that resistance training reduces blood pressure (34) and modulates ACE gene expression (35). Human studies in this area are relatively scarce, but the scientific literature to date indicates that dynamic resistance training significantly lowers systolic, diastolic, and mean arterial pressure (36). The putative involvement of the RAS in fibrinolytic adaptations to RT is not thoroughly addressed in the literature, and additional research is warranted.

Endothelial function is enhanced by regular aerobic training, resistance training, and training regimens that combine

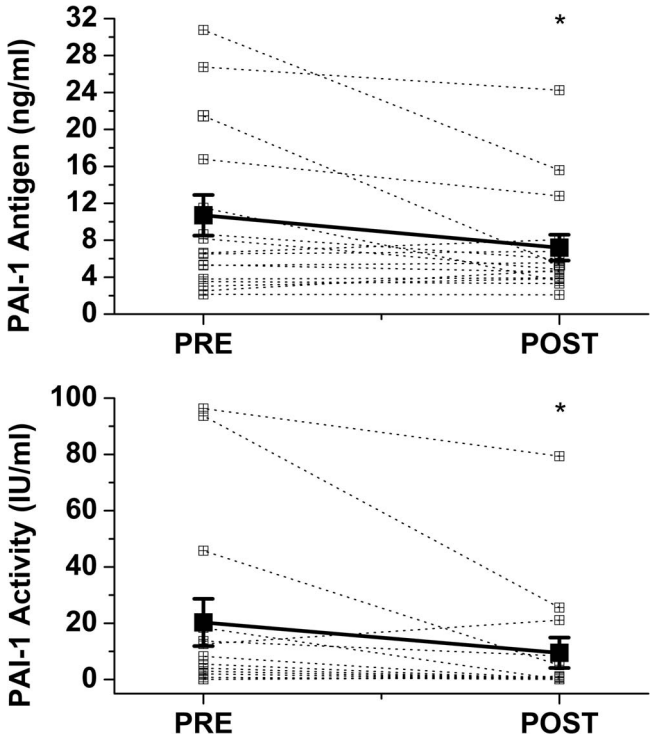

FIGURE 2—Plasminogen activator inhibitor-1. *Significantly different compared with PRE ($P < 0.05$). Shown are mean ± SE and values from individual participants. PRE, baseline; POST, after 8 wk of resistance training; PAI-1, plasminogen activator inhibitor-1.

both aerobic and resistance exercises (37). This adaptation is theorized to be related to exercise-induced increases in vascular shear stress, brought about by increased blood flow during exertion. Because the endothelium is a primary release site of tPA, this mechanism is theorized to lead to increased circulating levels of tPA after regular exercise training. tPA concentrations in the present study did not change after 8 wk of resistance training, potentially indicating that the exercise stimulus did not affect the vascular endothelium to the degree that it would likewise affect fibrinolytic activation. This may be due to the relatively brief training regimen, as most investigations that show endothelial improvement after resistance training are longer than the present study (median, 12 wk) (37). It is also known that endothelial release of tPA is affected by age (7). Perhaps the participants in our study, with relatively young and healthy endothelial cells, were unlikely to exhibit pronounced changes in endothelial function during training. As endothelial function was not assessed in the present study, this is strictly conjecture and warrants additional study.

Coagulation potential in the present study was assessed by measuring blood levels of proteins from all three pathways of the coagulation cascade. The literature reveals very little information regarding the effects of strength training on activity of the coagulation cascade, but a number of studies report conflicting information with respect to the influence of aerobic exercise on blood coagulation. Inverse relationships between physical activity level and factor VIII have been reported (10), and factor VII was reduced in sedentary men after 3 months of aerobic training (38). However, other investigations show no correlation between physical activity and factor VII or factor VIII concentrations (39,40). Fibrinogen has been shown to decrease (41), not change (42), or increase (43,44) after aerobic exercise training in various populations. The present study indicates that factor VII, factor VIII, and fibrinogen are not affected by 8 wk of resistance training. Additional studies are needed to replicate these findings and to further explore potential mechanisms through which exercise training may influence coagulation potential.

The following limitations must be considered when interpreting the results of the current study. First, the hemostatic variables under examination may be influenced by the composition of one's diet (45) and consumption of ethanol (4). The present study did not track or control for diet or alcohol, and thus cannot assess their potential influence on the reported outcomes. Future research would benefit from dietary analysis, particularly with respect to fat and carbohydrate intake, alcohol consumption, and fasting insulin levels. Furthermore, results of the present study are from a mixed sample of young men and women. Biological sex is known to influence some hemostatic parameters (46), but it is not clear if sex modulates hemostatic adaptations to exercise training. Future research should attempt to compare matched groups of men and women, which was not possible in the present investigation because of the small number of men who completed the study. There is substantial interindividual variability in some of the blood markers of hemostasis. Previous research suggests that variables such as fibrinogen and PAI-1 may fluctuate more than 20% over the span of 3 months (47). Furthermore, others have identified seasonal variations in some of the variables under examination (48). Data were collected over the span of several months in the present study, in a geographic location that experiences dramatic environmental changes in varying seasons. We cannot exclude the possibility that of some of the hemostatic results reported here were affected by seasonal and/or normal biological variations. Finally, the mechanisms that underlie the PAI-1 adaptations depicted in this study are not clear. It is recommended that future research assess training-induced changes of the RAS and explore the role they may play in modulating fibrinolysis after regular resistance exercise training.

In conclusion, this study explored the influence of regular resistance training on various blood markers of coagulation and fibrinolytic potential in healthy adults. Eight weeks of regular resistance training had no effect on fibrinolytic activation or coagulation potential, but significantly reduced fibrinolytic inhibition in healthy adults. These results suggest that regular resistance exercise may beneficially influence the risk of ischemic events.

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