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Effects of Ergometric Exercise on F-VIII Coagulant Activity in Mild and Moderate Haemophilia-A: A Chance to Reduce Injective Replacement Therapy

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Abstract: This study investigates the effect of ergometric exercise on F-VIII activity in mild and moderate haemophilia-A. The last study in this field was done in 1984. Despite of many results on healthy individuals and cardiac patients, the effect of exercise on coagulation parameters in bleeding disorder patients has not been well studied. 10 haemophiliacs (mean 24.5 year) were exercised on a bicycle ergometer according to Accepted Paediatric Protocol lasting 23-46 min. Blood samples were drawn before, 8 and 45 min post exercise. The average activity of F-VIII:c increases to 30.32 and 22.29% eight and 45 min post exercise, respectively. Increase of F-VIII:c activity was more pronounced in mild patients. Reduction in PTT, 45 min. post exercise, increase in vWF activity 8 min post exercise and increase in vW: Ag in both stage in to recovery were significant. It is concluded that ergometric exercise induce increase in F-VIII: c activity in mild and moderate haemophiliacs. Offering a suitable exercise programme in hemophilia-A not only improves their musculoskeletal system status but also increase F-VIII:c. Replacement therapy of factor deficient plasma is a kind of injective prophylaxis in severe haemophiliacs and exercise could be a suitable prophylaxis in mild and moderate haemophiliacs which could reduce the need of factor replacement therapy in these patients.

Key words: Coagulation, F-VIII complex, PTT, physiotherapy

INTRODUCTION

Frequency and severity of bleeding episodes in hemophilia-A vary considerably, not only between patients with identical levels of factor deficiency but also in the same individuals during different periods (Koch *et al.*, 1984). There is general agreement that physical exercise affects blood coagulation and fibrinolysis (Brown, 1979; Davis, 1976; El-Sayed, 1996; Koenig and Ernst, 2000). Exercise of varied intensity and duration have all induced significant increase in F-VIII coagulant activity and vWF (Corrall *et al.*, 1980) which persists into recovery (Rock *et al.*, 1997; Womack *et al.*, 2003; Paton *et al.*, 2004). This increase seems to be mediated via β -adrenergic receptor pathway as β -blockade blunts this process (Corrall *et al.*, 1980; Ikarugi *et al.*, 1999; Ingram *et al.*, 1977; Jilma *et al.*, 1997).

While both coagulation and fibrinolytic activity increase during exercise, during recovery the increase in F-VIII activity persisted, but fibrinolytic activity demonstrated a sharp fall (Lin *et al.*, 1999).

Koch *et al.* (1984) investigated the effect of exercise in hemophilia. This effect have not well studied in

coagulation disorder patients since then. Based on these data, our hypothesis was that exs. could increase F-VIII coagulant activity as well as acute phase reactive proteins such as von Willebrand's factor.

MATERIALS AND METHODS

Ten persons with mild and moderate haemophilia participated in this study. All subjects were non-smokers, free from medication for at least 3 months and free from any blood products replacement therapy for at least 7 days prior to and during the study. They had to refrain from exercise, the last 24 h preceding exs. testing. Subjects were not allowed to have caffeine containing foods and Drinks, bananas and cereals for 12 h before exercise to avoid increases in plasma catecholamines (Andrew *et al.*, 1986; Weiss *et al.*, 1998a).

Eight participants had mild and two had moderate F-VIII deficiencies. They exercised according to Modified Accepted Pediatric Protocol (James *et al.*, 1980) because of low exercise tolerance in these kinds of chronic patients. Blood pressure and pulse rate were measured

prior to (before the first blood sampling) and at 3 min intervals during the protocol. The protocol consisted of constant pedaling speed of 60 rpm, beginning by 5 min pedaling at 200 kg m min⁻¹ for a warm-up period. The work load was increased by 100 kg m min⁻¹ every 3 min until one of the following events happened voluntary exhaustion, exceeding systolic blood pressure over 200 mm Hg, or exceeding predicted maximal heart rate in each individual age.

All tests were performed between 9 to 11 am to avoid result discrepancies due to circadian rhythm of fibrinolysis (Prisco *et al.*, 1998). Pre-exercise samples were obtained ~15 min prior to the onset of the test. The first post-exercise sample were drawn 8-10 min following the cessation of exercise, since the previous studies of the time-course of exercise-related in F-VIII activity demonstrated maximal activity 5-10 min after exercise (Hansen, 1990; Wheeler *et al.*, 1986). The second post exercise sample were drawn 45 min post-exs. to evaluate F-VIII activity during the recovery period.

Blood samples were collected into plastic tubes containing 3.8% sodium citrate to give a ratio of nine parts blood to one part 3.8% sodium citrate. The blood was immediately transferred to polypropylene tubes and centrifuged for 15 min at 2000 xg and stored at -80°C until further testing.

Laboratory methods: Coagulation activity of F-VIII as well as partial thromboplastin time (APTT) and prothrombin time (PT) were determined according to manufacturer's instructions (DIAGNOSTICA STAGO). vWF was measured by Helena aggregometer instrument and its antigen was tested by ELISA method (Stago kit).

The study was approved by the Ethical Commission of the Tarbiat Modares University and participants joined the study after informed consent was given.

Statistical analysis: Data were analyzed separately for each exercise test by ANOVA with repeated measures for main effect of exercise. When ANOVA revealed a significant effect, student's t-test was used for post hoc testing to examine the difference between values at baseline and post exercise samples.

RESULTS

When compared with rest values, VIII:c activity increase 30.32% and 22.95%, 8 and 45 min post-exercise, respectively (Fig. 1). The significance was near the probability value. PTT decreases 2.52 and 3.24 sec, 8 and 45 min post-exercise, respectively. The significance was about the differences between pre and 45 min post-exs. values (Fig. 2).

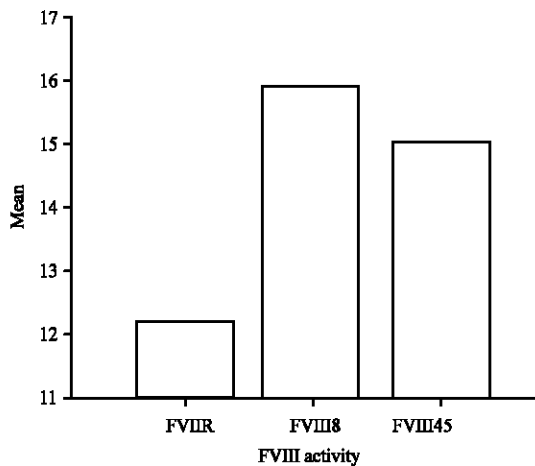


Fig. 1: F-VIII activity pre-exercise (FVIIIr), 8 (FVIII8) and 45 (FVIII45) min post-exercise

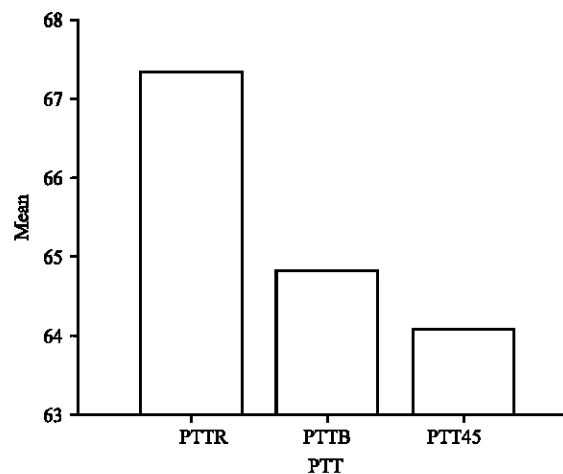


Fig. 2: PTT, pre-exercise (PTTR), 8 (PTT8) and 45 (PTT45) min post-exercise

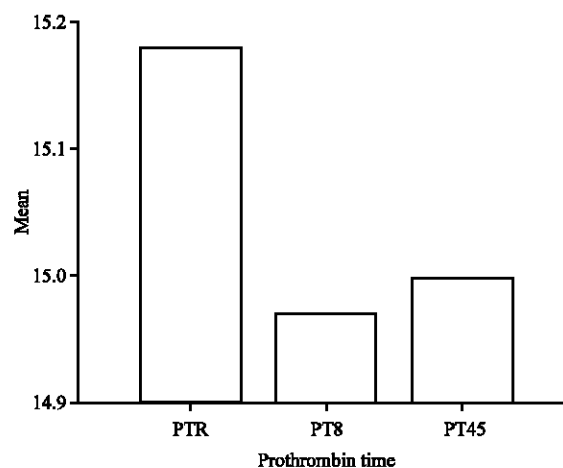


Fig. 3: PT, pre-exercise (PTR), 8 (PT8) and 45 (PT45) min post-exercise

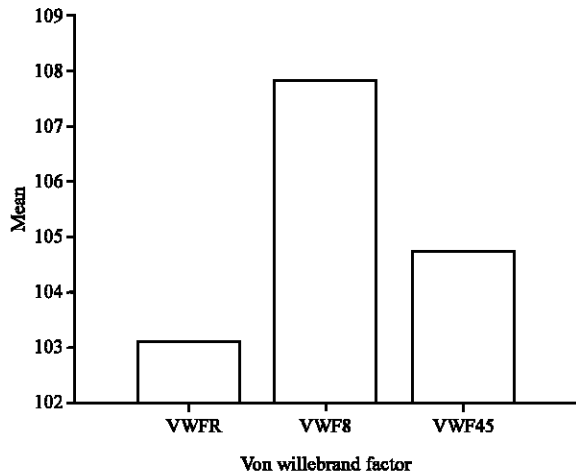


Fig. 4: VWF Activity pre-exercise (VWFR), 8 (VWF8) and 45 (VWF45) min post-exercise

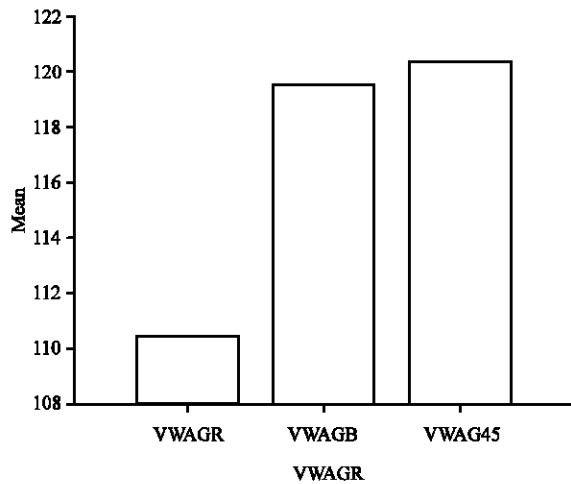


Fig. 5: vWF Antigen pre-exercise (VWAGR), 8 (VWAG8) and 45 (VWAG45) min post-exercise

Table 1: Haemostatic parameters before, 8 and 45 min post-exercise

Time of sampling	Mean±SEM		
parameter	Before exercise	8 min post-exercise	45 min post-exercise
F-VIII:c	12.2±3.8	15.9±5.24	15±4.93
vW:Ag	110.6±8.79	119.5±8.13	120.3±9.36
vWF	103.1±7.83	104.8±8.94	107.94±8.04
PT	15.18±0.41	14.97±0.55	15±0.34
PTT	67.36±5.12	64.84±5.25	64.12±5.05

No significant changes were evidenced in PT in response to exs. (Fig. 3). vWF activity significantly increased ($p = 0.02$), 8 min post-exs. and remain elevated after the 45 min of recovery (Fig. 4). vW:Ag significantly increased ($p = 0.02$), 8 min post-exs. And remain significantly elevated ($p = 0.03$), after 45 min in recovery, (Fig. 5). (Or) All data is represented in (Table 1).

DISCUSSION

Exercise consistently induces increase in the factor VIII complex in healthy individuals (El-Sayed, 2000; Koenig and Ernst, 2000; Kopitsky *et al.*, 1983), however, the magnitude of these changes varied considerably in reported literature. That may be due to lack of uniformity or quantitation of the intensity, duration and type of exercise. Andrew *et al.* (1986) has believed that exercise can be accurately quantitated and future investigations should provide a reproducible model for inducing consistent alterations in the VIII complex and fibrinolytic system, the idea we finally hope to find in hemophilia.

Koch *et al.* (1984) has reported the increase in VIII :c and VIII :Ag in four mild but not severe hemophiliacs. According to her experiences that severity of disease could influence the expected responses, in this study only mild and moderate patients were used and severes excluded.

The mean time in koch's study was 7.2 min (4-13 min) and the mean age was 11.6 years (8.3-15.5 years). In present study the mean time and age were 37.4 min (23-46 min) and 24.5 years (17-38 years), respectively. Increase in time may be due to higher tolerance in our older participants. We observed 30.32 and 22.95% increase in VIII:c, 8 and 45 min post-exs. Probability value was near 0.05 because of fewer cases as confirmed by β -65%. Koch has reported only 15% increase in VIII :C activity in the peak of exs performing. The higher VIII :C increase in our study could attribute to:

Age-related effects on plasma levels of haemostatic factors have been reported previously. Aging may well influence the functional capacity of endothelial cells to release the various products under stimulated conditions. Surprisingly enough, no differences in the magnitude of the exs induced haemostatic changes were observed by Van den Burg *et al.* (1995) in three age categories. Four years later in another investigation, he has reported that physical conditioning resulted in a more pronounced increase in vWF and FVIII:c in 20-45 year (Van den Berg *et al.*, 2000). Therefore, our patients include in the appropriate age category. Perhaps the most benefits of exercise in haemophiliacs also could reveal around this range of ages.

Weiss *et al.* (1998b) concluded, prolonged exercise is necessary for exs-induced activation of coagulation. A longer duration in the same exercise protocol may be responsible for higher F-VIII levels in present study. Achieving higher levels of F-VIII may need appropriate timing in exercise protocols.

By decreasing FVIII level in participants, increasing the post-exs levels, diminished. Therefore, severity of

disease influences the effect of exs. induced activation of coagulation. Two moderate (VIII:c = 2%) and one mild (VIII:c = 8%) hemophilic had any changes in FVIII activity in present study, so, the significance in VIII:c increase of only four patients in Koch *et al.* (1984) study may be resulted from the higher VIII:c basic values. The least increase in F-VIII:c belong to moderate patients (from 0%) and the highest increase was happened in mild forms with higher basic VIII:c activity (up to 131%).

There is probably more sites of F-VIII synthesis in mild forms that is responded to exercise or uncertain conditions. The highest increase in mild affected patients emphasized on the hypothesis that exs. induce activation of already circulating but inactive precursor F-VIII, not release of stored or freshly synthesized (El- Sayed, 1996).

Major increase in VIII:c activity occurred 8 min post-exs., with no sampling in the peak of protocol performing. These results are in agreement with Davis (1976) reports showed the peak F-VIII activity, 5-10 min post-exs. Davis (1976) and Wheeler *et al.* (1986) demonstrated the highest value of F-VIII:c and factor VIII:Ag exactly 8 min post-exs.

The increase in VIII:c activity persisted into 45 min recovery in this study. comparable results were reported by many investigators last either, up to 24 h post-exs. In healthy subjects (Lin *et al.*, 1999), or upto 120 min in haemophilics (Koch *et al.*, 1984).

As coagulation proteins like F-VIII:c has relatively short half-lives and the time of laboratory tests performing wasn't accurate, part of nonsignificance may be due to loss of activity during this unexpected periods.

Changes in PTT were 2.52 and 3.24 sec, 8 and 45 min post-exs., respectively. Therefore F-VIII increase influence the laboratory assays that reflects in intrinsic coagulation pathway. The main finding of Chicharro *et al.* (1995) was the decrease found in APTT (2.4 sec) persisted after 30 min of recovery only after high intensity exercise (Chicharro *et al.*, 1995). In contrast, it returned to pre-exercise levels when exs. performed at a lower intensity. In present study such parameter fortunately remains elevated even after 45 min in recovery. Weiss *et al.* (1998b) were also documented a significant shortening of the PTT after swimming, cycling and running. Van den Berg *et al.* (1997 and 2000) reported that individuals with a higher degree of physical activity had shorter clotting times. Further investigations is recommended in hemophilia. Weiss *et al.* (1998a) also reported a significant shortening of aPTT compared with baseline after moderate and very heavy exercise.

There were no significant changes of PT, while this shortening would be useful for F-VIII inhibitor haemophiliacs.

Significantly elevated vWF ($p = 0.002$) was detected 8 min post-exercise. A considerable increase in vWF after exercise related to moderate patients (two brother with FVIII:c level = 2%). Any changes in FVIII:c levels detected in them. Surprisingly enough these brothers have no bleeding episodes in routine daily living activities and one of them used to inject FVIII concentrates only for surgeries. By decreasing FVIII:c level, vWF activity and antigen increase. One mild patient with VIII:c level = 9% had 63% vWF activity over the normal value. A case with FVIII:c = 2% had vW:Ag = 112% while another with VIII:c = 14% showed vW:Ag = 80%. No significant inverse correlation revealed, but it is probable that a molecular compensation occur in F-VIII complex. Obviously, further investigation is recommended.

CONCLUSIONS

Despite of limited daily living and recreational activities recommendation in hemophilia population as a fear of increasing bleeding episodes, performing a suitable and safe exercise programme, particularly in mild and moderate forms, not only improves their musculoskeletal system status and increase dynamic joint support, but also augment their coagulation via increase in F-VIII coagulant activity.

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