Effect of Moderate Intensity Exercise on Hemostatic Capacity in Adults with Hemophilia A and B: Pilot Study

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INTRODUCTION

- Impact of exercise on both primary and secondary hemostasis has been well defined in individuals without an inherited coagulation defect[1,2,3]
- We are evolutionarily designed to enhance thrombin generation in response to stress
- A recent study by our group showed that exercise improves hemostatic capacity in boys with hemophilia and that this response was particularly strong post-puberty[4]

OBJECTIVES

Primary Objective:
- To determine whether exercise affects hemostatic parameters in men (18-65 years) with hemophilia A (HA) and B (HB)

Secondary Objective:
- To assess whether the response varies according to age in adulthood

METHODS

- 13 HA and 9 HB patients were recruited from St. Michael's Hospital Hemophilia Clinic
- Study procedures were conducted at the Physiological Research Unit (PRU) of the Hospital for Sick Children (HSC)
- Samples for the following tests were collected pre-exercise, 5 minutes post-exercise, and 1 hour post-exercise: complete blood count (CBC), activated partial thromboplastin time (aPTT), factor VIII activity (FVIII:C), factor IX activity (FIX:C), VWF antigen (VWF:Ag), VWF ristocetin cofactor activity (VWF:RCo), platelet function analyzer (PFA-100®), thrombin generation time, and thromboelastography (TEG)
- Primary outcome variables: FVIII:C and VWF antigen (VWF:Ag)

Eligibility Criteria

Inclusion criteria

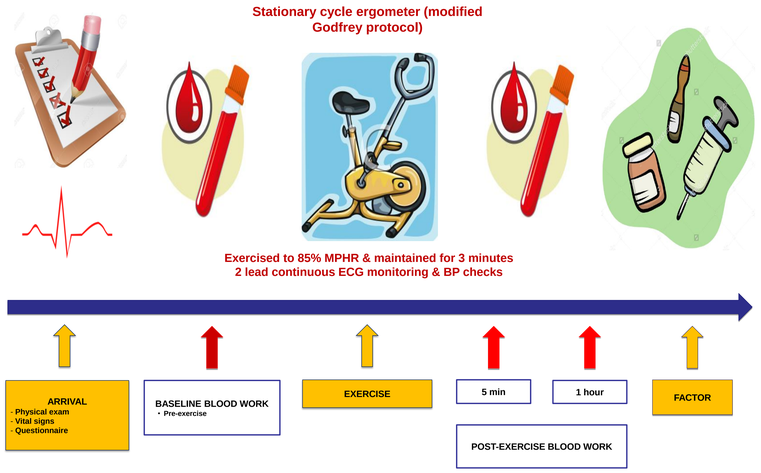
•Male (18-65 years) with HA (FVIII ≤10%) or HB (FIX ≤10%)

Exclusion criteria

•Positive FVIII or FIX inhibitor within past 5 years
•Co-existence of congenital bleeding disorder other than hemophilia (e.g. VWD)
•Concurrently enrolled in study investigating extended half-life coagulation factor product
•Prior history of CAD (or positive ECG) or pulmonary disease
•Regular beta-blocker, anti-platelet, or NSAID use
•Active infection or inflammatory condition (e.g. HIV, active Hepatitis B or C) or active cigarette smoking
•Bleed in any location within preceding 2 weeks or lower limb musculoskeletal bleed within preceding 4 weeks prior to protocol
•Limited exercise tolerance for any reason

METHODS (CONTINUED)

Figure 1. Timeline of Protocol



Statistical Analysis

- Impact of exercise on changes in each clotting parameter over time was evaluated by performing repeated measures analyses under the linear mixed model framework
- Statistical significance was defined as a p value of < 0.05
- Bonferroni correction for multiple comparisons was applied to the primary outcome variables VWF:Ag and FVIII:C
- All analyses were separately performed for HA and HB patients using SAS 9.4

RESULTS AND DISCUSSION

Participants

- 22 subjects recruited: 13HA – 3 mild, 6 moderate, 4 severe, 9 HB – 6 moderate, 3 severe
- Median age at study participation: HA – 33 years (range 20-55), HB – 37 years (range 18-64)
- Mean duration of exercise to achieve 85% MPHR: 10.1 (±2.6) minutes
- Mean duration of exercise: 14.5 (±2.5) minutes

Statistically Significant Hemostatic Changes

Baseline vs. 5 Minutes Post-Exercise:
- HA: platelet count (p<0.0001, 15.42% ↑), hematocrit (p=0.0001, 4.35% ↑), PFA-100 (COL/ADP: p<0.0001, 28.00%↓; COL/EPI: p=0.0004, 22.06% ↓), aPTT (p=0.0100, 5.45% ↑), VWF:Ag (p<0.0001, 32.20% ↑), VWF:RCo (p=0.0018, 30.28% ↑), FVIII:C (p=0.0050, 60.00% ↑)

- HB: platelet count (p=0.0004, 10.66% ↑), hematocrit (p=0.0182, 4.55% ↑), PFA-100 (COL/EPI: p=0.0015, 37.41% ↓), VWF:Ag (p<0.0001, 33.33% ↑), VWF:RCo (p=0.0005, 44.87% ↑), FVIII:C (p<0.0001, 56.90% ↑)

RESULTS AND DISCUSSION (CONTINUED)

Statistically Significant Hemostatic Changes (continued)

5 Minutes vs. 1 Hour Post-Exercise:
- HA: platelet count (p<0.0001, 16.79% ↓), hematocrit (p<0.0001, 6.25% ↓), VWF:Ag (p=0.0012, 17.31% ↓), VWF:RCo (p=0.0011, 24.65% ↓), aPTT (p=0.0011, 6.90% ↓), FVIII:C (p=0.0406, 25.00% ↓)

- HB: platelet count (p<0.0001, 12.84% ↓), hematocrit (p=0.0002, 6.52% ↓), aPTT (p=0.0053, 5.56% ↓), VWF:Ag (p=0.0006, 15.00% ↓), FVIII:C (p=0.0007, 18.68% ↓)

Baseline vs. 1 Hour Post-Exercise:
- VWF:Ag and FVIII:C levels remained significantly elevated for only HB participants (p=0.0080, 13.33% ↑ and p=0.0013, 27.59% ↑, respectively) (see Figures 2 and 3)

Figure 2. Hemophilia A and B box plots by time for FVIII:C

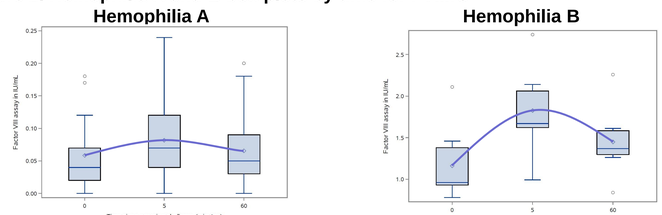
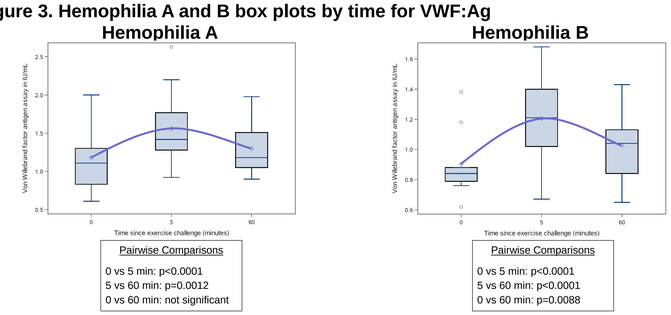


Figure 3. Hemophilia A and B box plots by time for VWF:Ag



Discussion

- For the first time, a sustainable increase in VWF:Ag and FVIII:C was found in men with HB in contrast to men with HA
- This suggests the possibility of a differential hemostatic response to moderate exercise, which may explain the variation in bleeding phenotype
- In general, age did not influence the hemostatic response to exercise
- The study is limited by the small sample size and selection bias (younger, physically fit participants)

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