The extent of von Willebrand factor antigen rise during moderate physical activity modulates FVIII half-life in severe haemophilia A subjects.

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TOPIC: Clotting Factor Concentrates

INTRODUCTION

- **BACKGROUND**

Guidelines for managment of haemophilia recommend that subjects perform regular and appropriate physical activity[1,2]. In moderate and mild haemophilia A subjects, exercise increases endogenous factor VIII (FVIII) half-life[3,4]. In severe haemophilia A subjects, exercise induces a transient increase of von Willebrand factor Antigen (VWF:Ag) with no significant difference in FVIII mean half-life. VWF:Ag increase is notably higher in non-O blood group subject[5].

- **AIMS**

To evaluate the impact of VWF:Ag on FVIII PK (null mutations) in young adults with severe haemophilia A performing moderate-intensity physical activity.

METHODS

- **STUDY PROTOCOL**

The study involved 4 visits by participants : two 9 h visits (visit 1:«rest» and visit 2: «exercise», and two 1 h visits, the following morning (Fig. 1). Blood specimens were collected before infusing FVIII and at 15 min, 1h, 3h, 6h, 9 h and 24h. During the visit 1, participants remained sedentary, until 24h post FVIII infusion. Participants performed 4 sessions of exercises during the visit 2: 2x15 min stationary cycling and 2 x treadmill walking at 65% of maximun heart rate (± 10bmp).

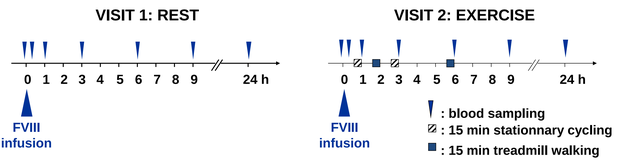

Figure 1: Study design. FVIII concentrate administrated at time=0

- **LABORATORY ASSAY**

FVIII activity was measured using the one-stage clotting assay and VWF:Ag was measured with an immunoturbidimetric assay on platelet-poor-plasma. Differences between rest and exercise were compared with two-way ANOVA with Bonferroni post-test and Wilcoxon matched-pairs signed -Ranks test. A p value <0,05 was considered significant.

•SUBJECT RECRUITMENT: The study was approved by the medical Ethics Committee of the CHU Sainte-Justine. All subjects gave written, informed consent for participation in the study.

INCLUSION CRITERIA

- FVIII <1%, null mutation
- 18-30 years old
- on a prophylaxis treatment regimen with recombinant FVIII product
- a Haemophilia Joint Health Score (HJHS) <15 at the knee or ankle joint

EXCLUSION CRITERIA

- presence of inhibitors
- clinical signs of active bleeding

RESULTS

- **SUBJECTS CHARACTERISTICS:** 12 young adults age 19 to 31 years (median: 23,5 years) participated to visit 1 and visit 2. Median age was 23.5 y (range 19-31 y). Median HJHS score was 4.5 (range 0-13), maximum unilateral knee or ankle joint score ranged from 0-12 (median 3.5), median global gait score was 1 (range 0-4). Median body mass index (BMI) was 23.7 kg/m² (range 19.9–32.9 kg/m²). FVIII prophylaxis varied from 1-7/wk (median 7/wk) of 500-2000 IU (median 600 IU), and 6-32 IU/kg (median 8.5 IU/kg/day). All patients used Helixate FS®, except one, who used Xyntha®.

- **ABBREVIATED PK OF FVIII ACTIVITY AND VWF :Ag LEVELS AT REST AND DURING MODERATE PHYSICAL ACTIVITY**

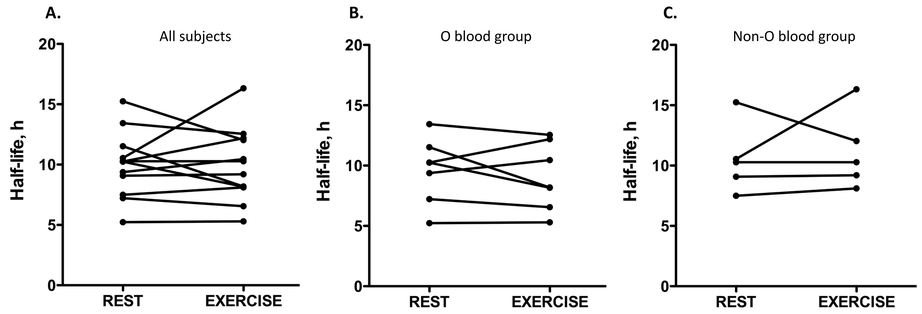

Figure 2: Individual subjects half-life at rest and following exercise. **(A)** All subjects (n=12). **(B)** Subjects with O-blood group (n=7). **(C)** Subjects with non-O blood group (n=5).

- Mean half-life ranged from 10h13±2h42 at rest to 9h36±3h09 (p=0,413) with exercise in all subjects; from 9h51±2h45 to 8h22±2h39 (p=0,1562) in O blood group subjects; and from 10h45±2h52 to 11h19±3h15 (p=0,6250) in non-O blood group subjects

- Exercise decreased FVIII half-life in 5/12 subjects and increased FVIII half-life in 6/12 subjects

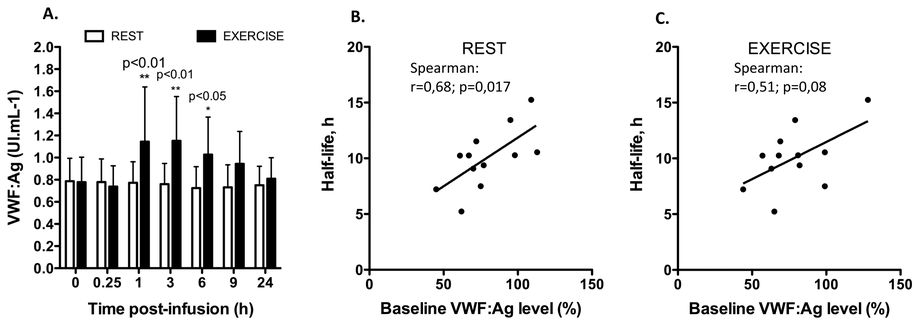

Figure 3: VWF:Ag level at rest and with exercise. **(A)** Mean VWF:Ag post-FVIII infusion at rest compared with exercise**. (B)** Correlation between baseline VWF:Ag level with FVIII half-life at rest or **(C)** following moderate intensity physical activity.

- The mean fold increase in VWF:Ag was 1,5 fold 1h (p<0,01) and 3h (p<0,05) post-FVIII infusion at exercise as compared with rest and 1,4 6h post-FVIII infusion (p<0,05)

- FVIII half-lives measured at rest and following exercise both correlated with baseline VWF:Ag

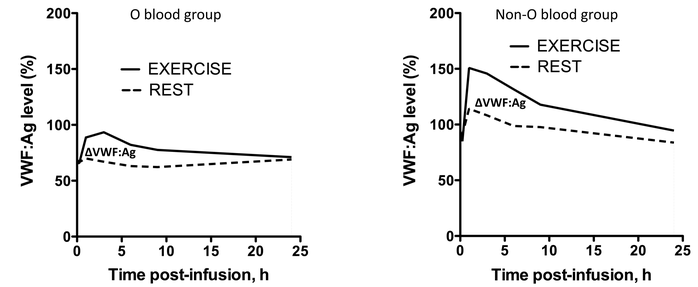

Figure 4: Time course of VWF:Ag level in function of ABO blood group.

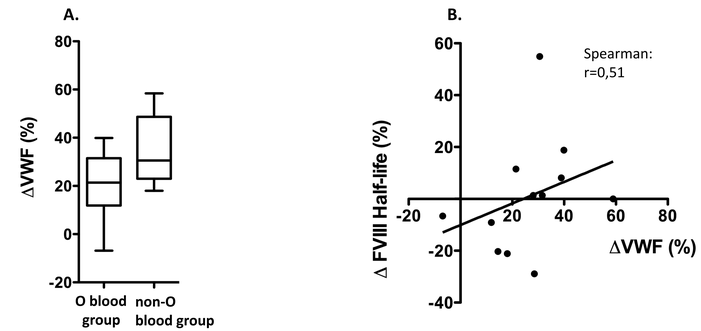

Figure 5: Increase of VWF:Ag level with exercise. **(A)** Changes in function of ABO blood group. **(B)** Relationship between change in VWF:Ag and FVIII half-life when performing exercise as compared with resting state (all subjects , n=12).

- Subjects with non-O blood group had a greater increase in VWF:Ag (+34%, range: +18 to 58,4%) when performing moderate physical activity as compared to subjects with O-blood group (+20,1%, range: -6,85 to +39,9%)

- A threshold value of +24% in VWF:Ag level discriminated subjects with increased half-lives from subjects with decreased half-lives

CONCLUSIONS

The extent of VWF:Ag rise during moderate-physical activity contributes to FVIII half-live variation. This pilot study suggests a potential influence of ABO blood group in the modulation of therapeutic FVIII replacement through a higher VWF:Ag rise during exercise. The limitation of the study being the small sample size, a larger study is currently being conducted in order to validate these results.

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