PROTEIN S: ASSAYS, ASSOCIATED THROMBOSIS RISK AND PF24RT24

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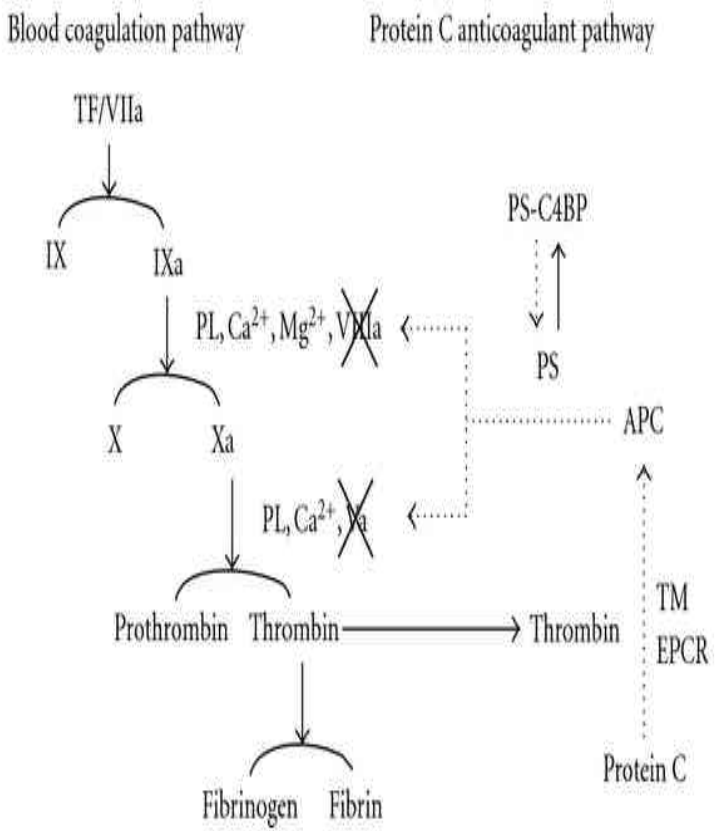
Points to Cover

- Protein S Assays
  - Complexity
  - Applicability to normal populations and patients
- Assays in S/DP vs. PF24RT24
- Clinical significance of protein S levels

Protein S Activity Measurement

- Protein S activity is assessed by measuring its ability to catalyze protein APC inhibition of factor Va
- False positives common
- Levels differ by gender, hormones
- Assay affected by:[1]
  - Method and Instrumentation[2]
  - APC resistance/FV Leiden
  - Lupus anticoagulants
  - High FVIII, FVII, or FII
    - PS activity decreased by 31% (StaClot) and 7.6% (IL) when normal plasma spiked with FVIII to 300%[3]



[1]Goodwin et al, Arch Pathol Lab Med 2002; [2]NASCOLA, Am J Clin Path, 2005; [3]2001 CAP Survey

Is Protein S in S/DP and PF2RT24 the same?

Evidence for SD processing effect on PS function with a resulting dysfunctional molecule

1. Measurement of protein S activity and free antigen in 2 pools of S/DP (PLAS+SD)[1]
   - Pool 1: 24.8%/126.8%; Pool 2: 15%/97.5%
2. Comparison of US and EU products. In US (PLAS+SD)[2]
   - Batch 1: 20%/131%; Batch 2: 15%/119%

[1]Flamholz et al, J Clin Apheresis, 2000; [2]Salge-Bartels et al, Transfusion Med, 2006.

Risk of TE with low Protein S

- Variable rate of thrombosis in family studies
  - Important cofactors such as FV Leiden
- Risk in epidemiologic studies modest at best
- MEGA study[1]
  - large case control study VTE risk (~5000 each)
  - 2471 patients/2940 controls with plasma sample
    - No increased risk with <2.5th %ile compared to 2.5th-97.5th (total and free)
    - With free protein S could obtain an increased OR if lowered cut-off but wide CI due to small patients in set

[1]Ribeiro et al, ASH abstract 2011

My conclusions

- Protein S antigen and activity are modestly decreased (~ 10%) in PF24RT24
  - Clinical significance likely minor
- Markers of coagulation in PF24RT24 do not support an overall increase in activation
- "Accurate" measurement of protein S activity is challenging, particularly in patients
- SD treatment (in PLAS+SD) may decrease protein S activity